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Original Article

Therapeutic Potential of Gemfibrozil in Mitigating Nonalcoholic Steatohepatitis Associated with Dysmetabolic Conditions

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ABSTRACT

Background: Dysmetabolic condition-associated liver disease has recently become the most common type of liver disease, with high rates and serious health impacts, especially nonalcoholic steatohepatitis NASH. Hepatic steatosis is known as the key pathophysiological characteristic of NASH. **Objective:** This study evaluates the therapeutic potential of gemfibrozil as a curative and preventive treatment option for NASH. Saroglitazar, the only approved therapy for NASH in India, served as a comparator to assess gemfibrozil's benefits. **Method:** Thirty-six *Wistar rats* were randomly assigned to six groups. The control group received a standard diet, while the disease control group was fed a high-fat diet (HFD) to induce NASH. The remaining four groups were allocated to curative and preventive treatment arms; these groups received gemfibrozil or saroglitazar with HFD as per the study design. The study assessed the therapeutic effects of gemfibrozil and disease progression by measuring biochemical markers such as serum enzymes, lipids, and metalloproteinase expression. The abundance of hepatic stellate cells was determined through gene and protein expression analysis. Histopathological evaluation assessed changes in hepatic morphology. **Results**: NASH progression was marked by significant changes in serum lipid and enzyme levels and metalloproteinase expression. The disease control group exhibited increased caspase-3 antibody and Apo A4 gene expression. Histopathological analysis showed that HFD induced moderate-to-severe hepatocytic changes. Treatment with gemfibrozil or saroglitazar significantly reduced elevated biochemical levels to near-normal and restored hepatic morphology by inhibiting lipogenesis and modulating lipid metabolism in both preventive and curative settings. Caspase-3 and Apo A4 expression demonstrated recovery trends compared to the disease control group, although no significant correlation was observed. Extending the duration of treatment may further promote normalisation of protein and gene expression levels. **Conclusion:** In an animal model of dysmetabolic condition-associated NASH, gemfibrozil showed therapeutic potential compared with the approved therapy saroglitazar, supporting its potential as an alternative, cost-effective treatment option for further clinical studies.

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INTRODUCTION

Non-alcoholic fatty liver disease is now more common among people mainly due to lifestyle changes like consumption of high-fat foods and getting less exercise.[1] These behaviours are initially associated with lipid imbalance in serum and liver, obesity, and high blood sugar.[2,3] It slowly takes hold as fat quietly builds up in the liver, often without warning.[4] A subset of individuals progress to NASH, which promotes hepatic steatosis and may ultimately result in cirrhosis.[3] Liver ailments are becoming an ever-growing threat, with their burden and death rates climbing swiftly, particularly across developed nations.[5,6] In 2023, about 16.1% of people worldwide, or roughly 1.3 billion individuals, were living with metabolically associated liver disease. This number is expected to rise to about 1.8 billion by 2050, leading to significant health and economic challenges around the world.[5] Recent research shows that almost 40 percent of Indians may have metabolically associated liver disease.[6]

According to the pathogenesis theory, an initial trigger such as obesity, high blood fats, impaired glucose tolerance, diabetes, high insulin, or insulin resistance from metabolic disturbance causes fat to accumulate in the liver.[7,8] A second trigger, such as the release of inflammatory cytokines or oxidative stress, then leads

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to severe inflammation.[7] In contrast, multiple theories suggest that environmental, metabolic, and genetic factors all work together to cause and worsen NASH.[9]

Reportedly, Saroglitazar is the medicine authorised in India that is indicated for type 2 diabetes mellitus, NAFLD, diabetic dyslipidaemia, and noncirrhotic NASH.[10] Gemfibrozil has been indicated since 1981 for the treatment of hyperlipidaemia.[11] However, the potential of gemfibrozil in mitigating NASH associated with dysmetabolic conditions in different dose setups has not been clearly reported.

MATERIALS AND METHODS

Drugs

Drugs, i.e., gemfibrozil capsule 300 mg (brand name: Lopid 300), manufactured by Pfizer, and saroglitazar tablet 4 mg (brand name: Lipaglyn), manufactured by Zydus, were procured from a one-chemist pharmacy, Thane, Maharashtra, India.

Animal and feed

This study was conducted in accordance with the protocol approved (approval no. SCI/IAEC/2024-25/147, dated December 21, 2024) by the Institutional Animal Ethics Committee of Scitesla Private Limited, Navi Mumbai, under the oversight of the Committee for the Purpose of Control & Supervision of Experiments on Animals, Government of India.

Thirty-six *Wistar rats* (either sex), weaned at 3–4 weeks of age and weighing 30–65 g, were obtained from LACSMI Biofarms, Alephata, Pune, Maharashtra, India. The rats were housed at Scitesla Private Limited, Navi Mumbai, Maharashtra, India, three per cage, under controlled laboratory conditions: autoclaved corn cob bedding, a 12:12 light-dark cycle, temperature of 20–23 °C, and relative humidity of 30–70%. They had unrestricted access to tap water. Biochemical estimations and assessments of gene and protein expression were conducted at Scitesla Private Limited, Navi Mumbai, Maharashtra, India. Histological assessments were carried out at Unique Biodiagnostic Lab, Mumbai, Maharashtra, India

Study design

Thirty-six animals were divided using simple random sampling into six groups, with six rats in each group i.e. a normal control group, a disease control group, and four treatment groups receiving either curative or preventive interventions.

- Normal control (NC) group: Normal diet for 18 weeks
- Disease control (DC) group: High-fat diet (HFD) for 18 weeks
- Test (gemfibrozil) curative treatment (T-CT): HFD for 12 weeks; after week 12, gemfibrozil 25 mg/kg/day orally for 6 weeks along with HFD

Table 1: Composition of HFD and normal pellet diet.

HFD parameters	Values (%)
Moisture	8.00
Crude Protein	18.00
Crude Fat	35.00
Crude Fibre	6.00
Calcium	1.00
Phosphorus	0.50
Total Ash	6.00
Carbohydrates	35.00
Energy	5000 Kcal/kg
The composition of the normal pellet diet: Crude Fat 5.50%, Carbohydrates 65%, Energy 3500 kcal/kg	

- Standard (saroglitazar) curative treatment (S-CT): HFD for 12 weeks; after week 12, saroglitazar 4 mg/kg/day orally for 6 weeks along with HFD
- Test (gemfibrozil) preventive treatment (T-PT): Gemfibrozil (12.5 mg/kg/day) from week 3 and continued along with HFD for the remaining 15 weeks
- Standard (saroglitazar) preventive treatment (S-PT): Saroglitazar (2 mg/kg/day) from week 3 and continued along with HFD for the remaining 15 weeks

Curative Treatment groups (T-CT and S-CT) were fed an HFD for 12 weeks; after week 12, gemfibrozil (25 mg/kg/day, oral) or saroglitazar (4 mg/kg/day, oral) was administered simultaneously with the HFD for 6 weeks. Preventive Treatment groups (T-PT and S-PT) received gemfibrozil (12.5 mg/kg/day, oral) or saroglitazar (2 mg/kg/day, oral) from week 3 and continued along with HFD for the remaining 15 weeks. At week 19, rats were euthanized using CO_2, and their livers were removed for histopathological evaluation. **Table 1** shows the fat, protein, and carbohydrate content of the HFD and normal pellet diet.

Assessment of serum enzymes and lipids

Serum was analysed to measure total triglycerides (TG), low-density lipoprotein (LDL), and alanine transaminase (ALT) levels using an autoanalyzer (Model: EM200, Make: Transasia, India)

MMP-1 and TIMP-3 measures

Serum levels of MMP-1 and TIMP-3 were quantified using enzyme-linked immunosorbent assay (ELISA). Commercially available assay kits for MMP-1 (Develop, China; catalogue number: DL-MMP1-Ra) and TIMP-3 (Develop, China; catalogue number: DL-TIMP3-Ra) were utilised for the analysis.

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Gene expression by real-time quantitative reverse transcriptase PCR (qRT-PCR)

Total RNA was isolated with TRIzol reagent and subsequently converted to cDNA using the Two-Step RT-PCR Clone Kit. Quantitative PCR was performed on a 7500 Real-Time PCR System with the GREAT Real-Time SYBR PCR Kit. Relative mRNA expression levels were determined and normalised to GAPDH (Glyceraldehyde-3-phosphate dehydrogenase).

The genes and their corresponding primers were: GAPDH (forward: 5'-ATGACTCTACCCACGGCAAG-3'; reverse: 5'-CTGGAAGATCGTGATGGGTT- 3'); ApoA4 (forward: 5'-GTGAGGAGCCCAGGATGTTC-3'; reverse: 5'-GCTGGGTGAAGTAGTCCCAC -3').

Protein expression by Western blot

Cells were carefully lysed with RIPA Lysis and Extraction Buffer (Thermo Fisher Scientific) to extract total protein, and the resulting concentration was measured using the BCA assay (Thermo Fisher Cat No: 23227). The same amount of protein was loaded into each lane, separated on a 12% SDS-PAGE gel, and transferred to PVDF membranes (Bio-Rad). Membranes were blocked with a blocking agent (Thermo Fisher Cat No. 37543) and incubated overnight at 4 °C with primary antibodies against Caspase-3 (1:5000, Develop China) and β-Actin (1:5000, Develop China). Following incubation with an HRP-conjugated secondary antibody (1:5000, Develop China), the resulting protein bands emerged clearly when developed with an ECL Substrate Kit (Bio-Rad, Shanghai, China).

Histological analysis

Liver samples were fixed in 10% neutral buffered formalin for 24 hours at room temperature. Tissue sections were cut at 5 µm and stained with haematoxylin and eosin. Slides were examined at 400× magnification. Microscopic outcomes of hepatic sections were graded on a four-point scale: minimal (+1), mild (+2), moderate (+3), and severe (+4). This grading system was used to compare microscopic findings among groups, including micro- and macrovesicular changes due to cholesterol deposition, chronic inflammation in hepatic cells (yellow arrows), and inflammatory infiltrations (white arrows).

Statistical determinations

Results are presented as the mean ± standard error of the mean (SEM). In biochemical assessment, the statistical significance of differences among the treatment groups' arithmetic means was assessed using two-way ANOVA with Bonferroni post hoc testing in GraphPad Prism version 7. The statistical significance of differences in gene, protein, and MMP-1 and TIMP-3 expression in the treatment groups was assessed using one-way ANOVA with Bonferroni post hoc testing.

RESULTS

Assessment of serum enzymes and lipids

At week 12, serum TG levels were significantly higher in the DC group compared to the NC group (NC 78.00±4.6, DC 178.17±12.4 mg/dL, P<0.001), representing a 2.5-fold increase. This elevation persisted through week 18 (NC 116.00±4.0, DC 330.83±31.7 mg/dL). In the curative treatment groups (T-CT and S-CT), TG levels began to recover from week 14, with a significant improvement (P<0.001) from week 15 compared to the DC group (T-CT 134.00±6.9, S-CT 128.17±6.2, DC 272.67±13.2, NC 109.50±12.0 mg/dL). By week 18, curative treatment restored TG levels to normal (T-CT 100.67±8.4, S-CT 101.00±4.0, DC 330.83±31.7, NC 116.00±4.0 mg/dL). Preventive treatment (T-PT and S-PT) effectively prevented TG elevation from week 3 through week 18 (T-PT 85.17±14.7, S-PT 95.50±8.5, DC 330.83±31.7, NC 116.00±4.0 mg/dL), despite HFD administration.

Serum LDL levels were significantly higher (P<0.001) in the DC group compared to the NC group at week 12 (NC: 16.02±2.3, DC: 48.38±6.2 mg/dL). This elevation persisted with similar intensity through week 18 (NC: 45.48±4.3, DC: 100.52±3.3 mg/dL). Administration of the curative dose resulted in a downward trend in LDL levels from week 13 onward, leading to significant recovery by week 15 (T-CT 35.40±3.7, S-CT 23.22±6.0, DC 72.25±3.4, and NC 25.73±5.2 mg/dL, p<0.001) compared to the DC group. By week 18, LDL levels normalised (T-CT 28.83±2.8, S-CT 26.52±1.9, DC 100.52±3.3, and NC 45.48±4.3 mg/dL, p<0.001). The preventive dose administered to the T-PT and S-PT groups-maintained LDL levels near the normal range from week 3 to week 18 (T-PT 53.50±7.8, S-PT 50.93±3.5, DC 100.52±3.3, and NC 45.48±4.3 mg/dL). However, the preventive dose did not produce a statistically significant difference compared to the disease control group.

At week 12, serum ALT levels were significantly higher in the DC group compared to the NC group (NC: 26.0±8.2 mg/dL; DC: 98.8±18.9 IU/L, P<0.001). By week 18, this difference became more pronounced, with the DC group exhibiting markedly elevated ALT levels (NC: 27.6±4.9 IU/L; DC: 356.8±45.2 IU/L, P<0.0001). The curative dose significantly reduced elevated levels from week 14 onward (P<0.001), with values of T-CT 56.0±13.1, S-CT 34.9±9.8, DC 138.6±34.6, and NC 24.4±8.1 IU/L compared to the DC group. By week 18, the curative dose normalised ALT levels (T-CT 44.7±15.7, S-CT 28.7±9.5, DC 356.8±45.2, NC 27.6±4.9 IU/L, P<0.001). The preventive dose maintained controlled ALT levels from week 3 to week 18 (T-PT 35.2±12.2, S-PT 59.3±41.4, DC 356.8±45.2, NC 27.6±4.9 IU/L), showing a statistically significant difference from the DC group (P<0.001). **Figure 1** presents the effects of gemfibrozil or saroglitazar on serum TG, LDL, and ALT at different weeks.

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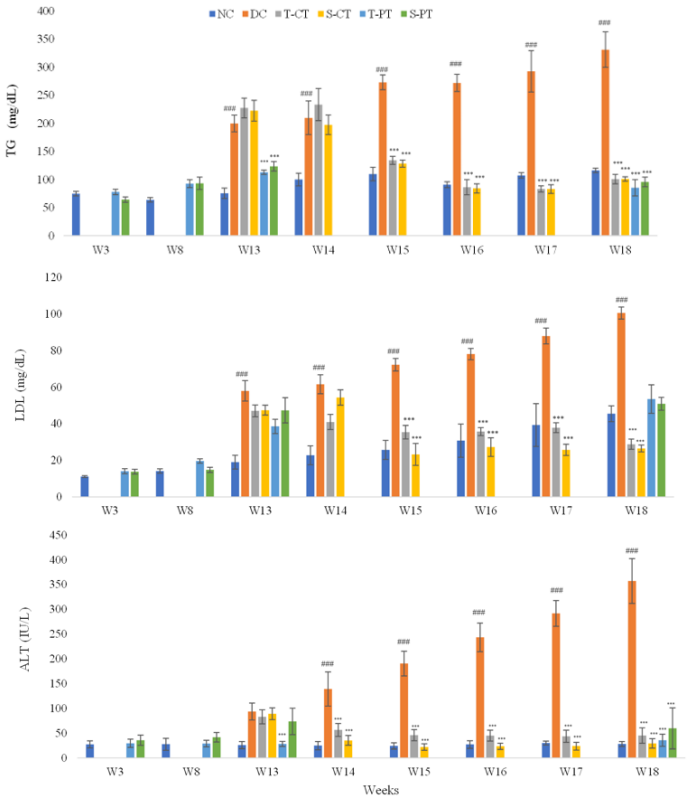


Figure 1: Effects of gemfibrozil and saroglitazar on TG, LDL & ALT. Data are presented as mean ± SEM (n = 6) and were analysed using two-way ANOVA followed by the Bonferroni post hoc test. Statistically significant differences were identified. #p<0.001 indicates comparison with the normal control group; ***p<0.001 indicate comparison with the disease control group.

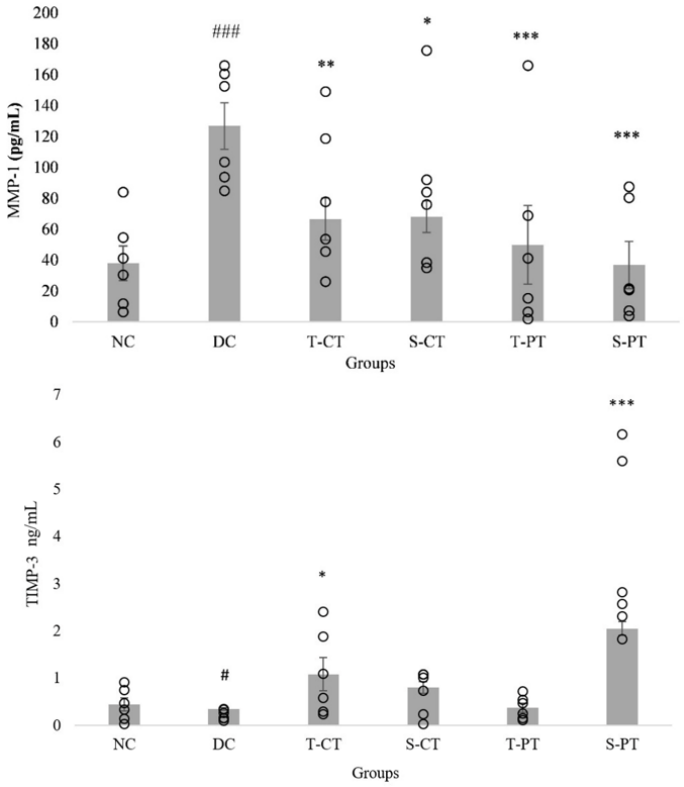


Figure 2: Effects of gemfibrozil and saroglitazar on MMP-1 & TIMP-3. Data are presented as mean ± SEM (n = 6) and were analysed using one-way ANOVA followed by the Bonferroni post hoc test. Statistically significant differences were identified. #p<0.001 indicates comparison with the normal control group; *p<0.05, **p<0.01 and ***p<0.001 indicate comparison with the disease control group.

Potential to ameliorate metalloproteinase enzyme alteration

MMP-1 and TIMP-3 levels were assessed at week 18. MMP-1 concentrations were significantly higher in the DC group compared to the NC group at week 18 (NC 37.90±11.23, DC 126.69±15.09 pg/mL, P <0.001). Curative treatments in the T-CT and S-CT groups significantly reduced MMP-1 levels at week 18 compared to the DC group (T-CT 66.48±13.63, S-CT 67.91±10.18, DC 126.69±15.09, NC 37.90±11.23 pg/mL, P <0.001). Preventive treatments in the T-PT and S-PT groups maintained MMP-1 levels near normal, with statistically significant differences from the DC group at week 18 (T-PT 49.78±25.44, S-PT 36.71±15.25, DC 126.69±15.09, NC 37.90±11.23 pg/mL, P <0.001).

At week 18, TIMP-3 levels were significantly reduced in the DC group compared to the NC group (NC 0.44±0.14 & DC 0.34±0.03 ng/mL, P<0.05). Curative treatment resulted in a marked recovery of TIMP-3 levels relative to the DC group (T-CT 1.08±0.35 ng/mL). The preventive dose in the T-PT group maintained TIMP-3 levels comparable to the NC group (T-PT 0.37±0.10 ng/mL), whereas the S-PT group exhibited a significant elevation in TIMP-3 levels compared to the DC group (S-PT 2.05±0.15 ng/mL, P<0.001). (**Figure 2**).

Gene expression (Apo A4)

Apo A4 transcription levels were measured using real-time qRT-PCR. mRNA levels were significantly lower in the DC group (0.04±0.04, P<0.001) compared to the NC group (1.01±0.01). Neither the curative dose of saroglitazar in the S-CT group (0.07±0.02) nor gemfibrozil in the T-CT group (0.08±0.01) improved mRNA levels relative to the DC group. Similarly, the preventive dose of gemfibrozil in T-PT (0.09±0.01) did not increase mRNA levels. However, saroglitazar in S-PT (0.59±0.15) resulted in a significant improvement (P<0.001) in mRNA expression. The effects of saroglitazar and gemfibrozil on Apo A4 mRNA expression are shown in **Figure 3**.

Protein (caspase-3) expression

Caspase-3 expression was significantly higher in the DC group (1.92±0.29 ARD, P<0.001) compared to the NC group (0.80±0.30 ARD). Saroglitazar curative treatment in the S-CT group reduced caspase-3 expression to baseline levels (0.79±0.05 ARD). Gemfibrozil curative treatment also reduced expression, though

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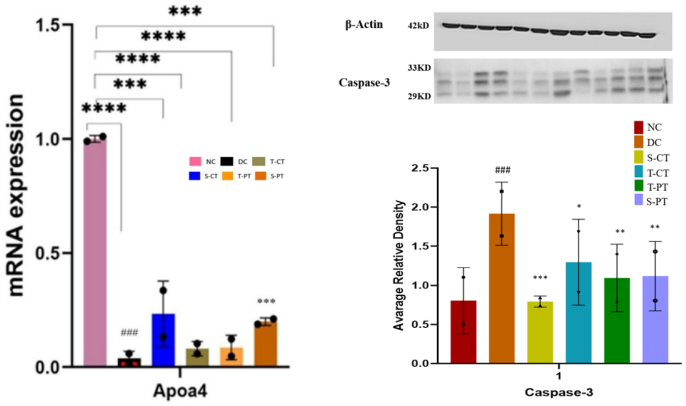


Figure 3: Effects of gemfibrozil and saroglitazar on mRNA (Apo A4) gene expression & optical density of caspase-3. Results are presented as Mean ± SEM (n = 6) and were statistically analysed using one-way ANOVA followed by the Bonferroni post hoc test. Statistically significant differences were observed: $^{###}p<0.001$, $^{##}p<0.01$ compared to the normal control group; $^{***}p<0.001$, $^{*}p<0.05$ compared to the disease control group.

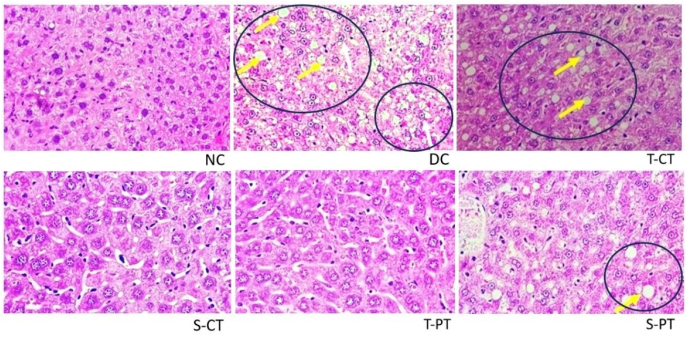


Figure 4: Effects of gemfibrozil and saroglitazar, at curative or preventive doses, on histological alterations. Moderate (+++) to severe (++++) hepatocytic micro- and macrovesicular changes (indicated by the yellow arrow) and mild (+) inflammatory infiltrations (indicated by the white arrow).

the decrease was less pronounced (T-CT 1.29±0.39 ARD, P<0.05 vs. DC group). These results suggest that extended therapy may be necessary for optimal recovery of protein expression. Preventive treatment with gemfibrozil or saroglitazar maintained caspase-3 regulation at significantly improved levels (T-PT 1.09±0.30, S-PT 1.12±0.31 ARD, P<0.01). The effects of gemfibrozil and saroglitazar on caspase-3 optical density are shown in **Figure 3**.

Histological analysis

Histopathological analysis showed that the NC group had normal liver architecture. In contrast, HFD administration led to moderate (+++) to severe (++++) hepatocytic micro- and macrovesicular changes (indicated by the yellow arrow) from cholesterol deposition and mild (+) inflammatory infiltrations (indicated by the white arrow), resulting in steatosis and inflammation, as shown in Figure 4. Curative treatment in T-CT and S-CT groups eliminated these alterations, indicating a protective effect against HFD-induced damage. Preventive treatment with T-PT and S-PT consistently prevented HFD-induced hepatocyte changes, and no abnormal pathological findings were observed in these groups.

DISCUSSION

A nonalcoholic steatohepatitis rat model was established using a high-fat diet containing at least 35% total fat. From weeks 12 to 18, the DC group demonstrated significantly higher blood levels of TC, LDL, and ALT compared to the NC group, indicating substantial disturbances in lipid and enzymatic metabolism. Histopathological analysis revealed hepatic steatosis in the DC group compared with the NC group. Including dedicated NC and DC groups from week 1 to week 18 allowed a comprehensive evaluation of HFD-induced changes in biochemical parameters and facilitated the identification of correlations with treatment interventions.

Dyslipidaemia, characterised by abnormal triglyceride, total cholesterol, and low-density lipoprotein (LDL) levels, is a major contributor to dysmetabolic conditions and significantly increases the risk of cardiovascular disease.[12] Evidence indicates that fibrates reduce triglyceride levels by 30% to 50%.[13] Fibrates exert their effects by decreasing LDL production, increasing fatty acid oxidation and triglyceride catabolism, enhancing lipoprotein lipase (LpL) synthesis, and reducing apolipoprotein C-III (apoC-III).[14] The therapeutic effects of gemfibrozil and saroglitazar were assessed in both curative and preventive contexts using rodent models of NASH. Rats fed a high-fat diet demonstrated significant changes in LDL and TC levels.

Changes in serum enzymes, specifically aspartate amino-transferase and alanine aminotransferase, indicate hepatic inflammation. These enzymes play a critical role in the pathophysiology of nonalcoholic steatohepatitis.[15] In this study, obese rats exhibited increased susceptibility to hepatosteatosis, as evidenced by elevated serum ALT levels. Gemfibrozil or saroglitazar administration significantly restored enzyme levels in the treatment groups, indicating protective effects on hepatic tissue.

Matrix metalloproteinase-1 is a key enzyme involved in collagen degradation and tissue remodeling.[16] Its expression is elevated in NASH rat models and is associated with fibrosis progression.[17] Tissue inhibitor of metalloproteinases-3 also modulates steatohepatitis, characterised by inflammation and lipid accumulation.[18] TIMP-3 functions as a natural inhibitor of enzymes such as a disintegrin and metalloproteinase (ADAM).19 ADAM is implicated in both inflammatory processes and insulin resistance.[19] Evidence suggests that reduced TIMP-3 levels may contribute to the pathogenesis of steatohepatitis. Gemfibrozil or saroglitazar restored serum MMP-1 and TIMP-3 levels to normal during curative treatment and kept them within safe limits during preventive treatment.

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Caspase-3 expression and activation are significantly increased in the liver tissues of animal models with NASH, contributing to hepatocyte cell death and disease progression.[20] In this study, caspase-3 expression was significantly higher in the Disease Control group. Curative treatment with saroglitazar reduced caspase-3 expression to near-normal levels. Curative treatment with gemfibrozil also reduced expression, although the decrease was less pronounced. These findings indicate that extended therapy may be required for optimal restoration of protein expression. Preventive treatment with either gemfibrozil or saroglitazar maintained caspase-3 regulation at significantly improved levels.

Hepatic Apo A4 expression is often elevated in steatosis, including steatohepatitis, suggesting a role in regulating hepatic triglyceride (TG) levels. Increased Apo A4 may promote the formation of larger lipoprotein particles, which can reduce hepatic TG content by enhancing TG export from the liver.[21] Apo A4 levels were significantly lower in the DC group. The study found that neither the curative dose of saroglitazar nor gemfibrozil affected mRNA levels. The preventive dose of gemfibrozil also did not increase mRNA expression. However, preventive treatment with saroglitazar significantly increased mRNA expression.

A high-fat diet (HFD) increases fatty acid synthesis and triglyceride accumulation in the liver, resulting in macrovesicular hepatic steatosis. Histopathological analysis revealed hepatocyte and liver tissue abnormalities in the disease group. Treatment with gemfibrozil or saroglitazar significantly reduced cholesterol deposition, hepatic inflammation, steatosis, and tissue damage.

CONCLUSION

The findings show that both gemfibrozil and saroglitazar effectively reduce hepatosteatosis caused by high-fat diet exposure in non-alcoholic steatohepatitis, with similar efficacy. Both agents offer significant curative and preventive benefits against enzymatic and lipid dysregulation, as well as hepatocyte infiltration and abnormalities. Treatment groups showed restored gene and protein expression, though the degree of recovery differed by intervention. Overall, gemfibrozil appears to be a cost-effective candidate for further clinical investigation in NASH treatment.

LIMITATIONS OF THE STUDY

Hepatocellular ballooning and fibrosis were not observed in the histological assessment. We did not assess a full panel of serum enzymes and lipid profile; instead, we assessed a brief panel.

ABBREVIATIONS

NASH: Non-Alcoholic Steatohepatitis; **HFD:** High-Fat Diet; **Apo A4:** Apolipoprotein A4; **NAFLD:** Nonalcoholic Fatty Liver Disease; **CPCSEA:** Committee for the Purpose of Control and Supervision of Experiments on Animals; **TG:** Triglyceride; **LDL:** Low-Density Lipoprotein; **ALT:** Alanine Transaminase; **MMP-1:** Matrix Metalloproteinase-1; **TIMP-3:** Tissue Inhibitor of Metalloproteinase 3; **qRT-PCR:** Quantitative Reverse Transcription Polymerase Chain Reaction; **GAPDH:** Glyceraldehyde-3-Phosphate Dehydrogenase; **PVDF:** Polyvinylidene Difluoride; **SEM:** Standard Error of the Mean; **ELISA:** Enzyme-Linked Immunosorbent Assay; **IAEC:** Institutional Animal Ethics Committee; **ANOVA:** Analysis of Variance; **SDS-PAGE:** Sodium Dodecyl Sulfate-Polyacrylamide Gel Electrophoresis; **ARD:** Average Relative Density; **ADAM:** A Disintegrin and Metalloproteinase; **LPL:** Lipoprotein Lipase; **HRP:** Horseradish Peroxidase; **ECL:** Enhanced Chemiluminescence; **TC:** Total Cholesterol;

AUTHOR CONTRIBUTIONS

Jain D.: Conceptualization, Methodology, Data interpretation, Writing – Original Draft & editing. Pithadia AB.: Review and supervision. All authors approved the final manuscript.

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CONFLICTING INTERESTS

The authors declare no conflict of interest.

ETHICS APPROVAL AND CONSENT

The study was approved (approval no. SCI/IAEC/2024-25/147, dated December 21, 2024) by the IAEC of Scitesla Private Limited, Navi Mumbai, which is registered with the CPCSEA, Government of India.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analysed during the study are available from the corresponding author on reasonable request.

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