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Sodium Orthovanadate (SOV) mitigates alcohol & alcohol plus high-fat diet (HFD)-induced hepatotoxicity in rats

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Abstract

Alcoholic fatty liver disease (AFLD) is a leading cause of chronic liver disease worldwide, contributing to significant morbidity and mortality. Despite its growing prevalence, no FDA-approved pharmacological treatments exist, leaving lifestyle modifications as the primary intervention. AFLD pathogenesis involves a complex interplay of lipid accumulation, oxidative stress, insulin resistance, and inflammation, highlighting the need for innovative therapeutic approaches. However, sodium orthovanadate (SOV), an inorganic vanadium-based compound, is a potent inhibitor of protein tyrosine phosphatases (PTPs), including PTP1B—a key regulator of insulin signalling and metabolic homeostasis. SOV has demonstrated insulin-mimetic properties and has shown promise in preclinical models of metabolic disorders. Given the emerging role of PTP1B in hepatic insulin resistance and lipid dysregulation, we hypothesize that SOV may offer therapeutic benefits in AFLD by modulating biochemical parameters and oxidative stress in liver. In this study, we investigate the effects of SOV in two rodent models of AFLD: (1) alcohol-induced liver disease and (2) high-fat diet plus alcohol-induced liver disease. We assess Biochemical Parameters like alkaline Phosphatase (ALP), aspartate amino transferase (AST), alanine amino transferase (ALT), lactate dehydrogenase (LDH), total bilirubin, cholesterol, uric acid, triglyceride. Tissue analysis like TBARS/MDA activity, Glutathione (reduced GSH) assay, Glutathione peroxidase (GPx) activity, Superoxide Dismutase, Catalase activity, and Histopathology to determine whether SOV can mitigate AFLD progression. Our research shows that SOV has promise as a treatment for fatty liver disease brought on by alcohol. Improvements in oxidative stress control,biochemical markers most likely mediate its hepatoprotective benefits. By uncovering the therapeutic potential of SOV, this study may pave the way for novel pharmacological strategies to combat fatty liver diseases.

Keywords: Sodium orthovanadate, Alcoholic fatty liver disease, Hepatotoxicity, High-fat diet, Oxidative stress

1. Introduction

Alcoholic fatty liver disease (AFLD) is a significant global health burden, representing a spectrum of liver disorders caused by chronic alcohol consumption. AFLD progression from simple steatosis to steatohepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma (HCC) is driven by a complex interplay of excessive lipid accumulation, oxidative stress, mitochondrial dysfunction, and inflammatory responses. Despite advances in understanding AFLD pathogenesis, effective pharmacological interventions remain limited, necessitating novel therapeutic strategies. One promising target for AFLD treatment is protein tyrosine phosphatase 1B (PTP1B), a key regulator of metabolic homeostasis that negatively regulates insulin receptor signalling. Overexpression of PTP1B has been associated with hepatic insulin resistance, endoplasmic reticulum stress, and excessive lipid accumulation, all of which contribute to the progression of alcoholic fatty liver disease (AFLD). Recent studies suggest that inhibition of PTP1B may improve hepatic insulin sensitivity, reduce liver fat accumulation, and mitigate oxidative stress-induced damage, making it a promising therapeutic target for AFLD [1,2]. Sodium orthovanadate (SOV), a potent and well-characterized PTP1B inhibitor, has shown potential in modulating metabolic dysfunctions in preclinical models of obesity, diabetes, and insulin resistance. SOV mimics the effect of insulin by promoting glucose uptake through GLUT4 translocation and suppressing hepatic lipogenesis by modulating key metabolic pathways, including AMPK and PI3K/Akt signalling. Furthermore, studies have demonstrated that SOV improves glucose homeostasis, reduces lipid accumulation, and mitigates oxidative stress-induced liver injury. Given its pleiotropic metabolic benefits, SOV has emerged as a potential

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candidate for alleviating AFLD-related pathologies. While extensive research has explored the therapeutic role of SOV in diabetes and metabolic syndrome, its application in AFLD remains underexplored. Preclinical studies indicate that SOV ameliorates hepatic steatosis and fibrosis in non-alcoholic fatty liver disease (NAFLD) models, suggesting its potential hepatoprotective effects in other liver disorders, including AFLD [3-5].

In this study, we hypothesize that SOV may exert hepatoprotective effects in AFLD by reducing hepatic lipid accumulation, oxidative stress, and inflammatory cytokine production. To test this hypothesis, we investigated the effects of SOV in two rodent models of AFLD: (1) alcohol-induced liver disease and (2) high-fat diet plus alcohol-induced liver disease [6,7]. We evaluated liver histopathology, lipid profiles, oxidative stress markers, inflammatory cytokines, and insulin sensitivity to determine the therapeutic potential of SOV in AFLD. By elucidating the role of PTP1B inhibition in AFLD, this study aims to provide novel insights into the potential of sodium orthovanadate as a pharmacological intervention for alcohol-associated liver disease.

2. Materials and methods

2.1. Animal procurement and maintenance

Swiss Albino Rats (180-200g) used in the study were purchased from a breeder registered with the CCSEA. The Institutional Animal Ethics Committee (IAEC) of Central Animal House at Desh Bhagat University in Mandi Gobindgarh gave its approval to the study's research protocol. In accordance with CCSEA, New Delhi, the animals were kept in a conventional laboratory setting with a controlled temperature (23±2), humidity (40±10), and light-dark cycle (12 hours each). The animals were given an unlimited water diet. A week was spent acclimating the animals prior to the start of the studies[8].

2.2. Fatty-liver disease model generation

A total of 72 animals were divided into two groups to induce fatty liver disease: Alcohol (ALC)-induced (n=36) and alcohol + high-fat diet (ALC + HFD)-induced (n=36). Each group was further subdivided into six subgroups (n=6 per subgroup): control, perse control, ALC, sodium orthovanadate (SOV) (5 mg/kg), SOV (10 mg/kg), and standard drug. The ALC group received alcohol 10ml/kg in drinking water continuously for 8 weeks, with solutions replaced every 24 hours. The ALC + HFD group received a high-fat diet (HFD) containing 60% kcal from fat (60% fat, 20% carbohydrates, 20% protein) along with alcohol 10ml/kg for 8 weeks. The HFD was prepared in-house and provided ad libitum. Body weight, food, and water intake were monitored weekly to ensure consistency in consumption and overall health [9].

2.3. Measurement of body weight to ensure health

To evaluate the general health status of the animals in the alcohol (ALC) and alcohol combined with a high-fat diet (ALC + HFD) groups, body weight was tracked during the trial. A digital weighing scale was used once a week to assess body weight. These assessments made sure that any notable shifts in eating habits or variations in weight, which could be signs of metabolic issues or declining health, were found. The effects of ALC and ALC + HFD on systemic health and metabolic balance in the model of fatty liver disease were assessed using data analysis [10].

2.4. Assessment of metabolic and liver function parameters in rat serum

At the end of the experimental period, blood samples were collected from the rats to assess various haematological and biochemical parameters. Blood collection was performed via retro-orbital plexus puncture using sterile glass capillary tubes under light anaesthesia to minimize pain and distress. Following collection, blood samples were transferred into appropriate tubes, with anticoagulant (EDTA)-treated tubes used for plasma separation and plain tubes for serum extraction. The samples were then centrifuged at 3,000 rpm for 10 minutes to obtain plasma and serum, which were subsequently stored at -80°C until further analysis. The biochemical parameters measured included markers of liver function—alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), and total bilirubin—as well as metabolic markers such as cholesterol, uric acid, and triglycerides. All biochemical analyses were performed using commercially available diagnostic kits according to the manufacturer's protocols. The assays were conducted using an automated biochemical analyzer (Reckon Diagnostics, Chandigarh; Span Diagnostics Ltd., Surat; and Erba Diagnostics, Baddi) to ensure accuracy and reproducibility of the results [11,12].

2.5. Assessment of tissue parameters

Tissue lysates were prepared by homogenizing the samples in ice-cold phosphate-buffered saline (PBS, pH 7.4) using a tissue homogenizer. The homogenates were centrifuged at 10,000g for 10 minutes at 4°C, and the supernatants were collected for further biochemical assays. Protein concentration was determined using the Bradford assay [13].

2.5.1. Lipid peroxidation assay (TBARS/MDA)

Lipid peroxidation was assessed by measuring thiobarbituric acid (TBA) reactive substances (TBARS). Briefly, 100 µL of sample was mixed with 2 mL of TBA (0.375%) and trichloroacetic acid (TCA, 15%) in 0.25N HCL. The mixture was heated at 95°C for 15 minutes and then cooled on ice. The reaction mixture was centrifuged at 3,000g for 10 minutes, and the absorbance of the supernatant was measured at 532 nm using a spectrophotometer. MDA levels were calculated using an extinction coefficient of 1.56×10^5 M^{-1} cm^{-1} and expressed as nmol MDA/mg protein [14].

2.5.2. Glutathione peroxidase (GPx) activity assay

The reaction mixture contained 50 mM phosphate buffer (pH 7.4), 1 mM EDTA, 1 mM NaN_3, 0.2 mM NADPH, 1 mM reduced glutathione (GSH), and 1 unit of glutathione reductase. The reaction was initiated by adding 0.25 mM hydrogen peroxide (H_2O_2). The decrease in absorbance at 340 nm due to NADPH oxidation was monitored for 3 minutes. One unit of GPx activity was defined as the amount of enzyme that oxidized 1 µmol of NADPH per minute, and results were expressed as U/mg protein [15].

2.5.3. Superoxide dismutase (SOD) activity assay

SOD activity was assessed based on the inhibition

of pyrogallol autoxidation. The assay mixture contained 50 mM Tris-HCl buffer (pH 8.2), 1 mM EDTA, and 0.2 mM pyrogallol. The reaction was initiated by adding the sample, and the change in absorbance at 420 nm was recorded for 3 minutes. One unit of SOD activity was defined as the amount of enzyme required to inhibit pyrogallol autoxidation by 50%, and results were expressed as U/mg protein [16].

2.5.4. Catalase activity assay

Catalase activity was measured based on the decomposition of H_2O_2. The reaction mixture contained 50 mM phosphate buffer (pH 7.0) and 10 mM H_2O_2. The reaction was initiated by adding the sample, and the decrease in absorbance at 240 nm was monitored for 2 minutes. One unit of catalase activity was defined as the amount of enzyme required to decompose 1 µmol of H_2O_2 per minute, and results were expressed as U/mg protein [17].

2.6. Histo-pathological examinations

For histopathological examination, animals will be sacrificed, and liver tissues were collected, fixed in 10% formalin, and embedded in paraffin. Sections (5 µm thick) were stained with haematoxylin and eosin (H&E) for general morphology. The stained sections were examined under a light microscope, and representative images were captured for comparative analysis [18].

2.7. Statistical analysis

ImageJ software and GraphPad Prism 8.4.2 were used for all statistical analyses. One-way ANOVA or the student t-test were used to examine the data, and $p < 0.05$ (*), $p < 0.01$ (**), and $p < 0.001$ (***) were used to indicate statistical significance.

3. Results

3.1. Experimental Design and Treatment Protocol

Non-Alcoholic fatty liver was produced by Alcohol model and Alcohol + High Fat Diet model for eight weeks. The test drug Sodium Orthovanadate (5 and 10 mg/kg) and Standard drug were administered to animals for eight weeks. At the end of the study on 57th day, the animal's blood sample were collected for biochemical studies and then the animals were sacrificed for tissue parameters assessment and histological studies (Fig. 1). Throughout this period, SOV was administered at doses of 5 mg/kg and 10 mg/kg body weight in both models. After the eight-week treatment, blood samples and liver tissues were collected for comprehensive analysis. Liver biochemical markers, tissue analysis were assessed from serum samples and tissue lysates,. Additionally, histopathological examination of liver sections was performed to observe morphological changes associated with liver damage and the protective effects of SOV. This study design allowed for a detailed assessment of SOV's therapeutic potential in mitigating alcohol- and diet-induced liver damage at both biochemical and histological levels.

3.2. Effect of SOV on body weight change in ALC & ALC + HFD-Induced hepatotoxicity model

The ALC-induced fatty liver group exhibited a significant increase in body weight following alcohol consumption, while SOV treatment (5 mg/kg and 10 mg/kg) led to a dose-dependent reduction in body weight, with SOV (10 mg/kg) showing a more pronounced effect. The standard drug resulted in the most significant weight reduction, surpassing both SOV-treated groups, though SOV (10 mg/kg) demonstrated a weight reduction effect comparable to the standard drug. Similarly, in the ALC + HFD-induced fatty liver group, alcohol and high-fat diet consumption significantly increased body weight, whereas SOV treatment dose-dependently reduced weight, with SOV (10 mg/kg) showing a more substantial effect than SOV (5 mg/kg). The standard drug exhibited the greatest weight reduction, with a more pronounced effect than SOV (10 mg/kg), though SOV (10 mg/kg) demonstrated a similar efficacy (Fig. 2). Overall, the ALC group exhibited more effective weight reduction compared to the ALC + HFD group, suggesting that alcohol alone may influence body weight changes more significantly, while the combination of alcohol and a high-fat diet may alter the metabolic response to treatment.

3.3. Effect of SOV on metabolic and liver serum biomarkers in ALC & ALC + HFD-Induced hepatotoxicity model

Alcohol exposure in the ALC group significantly el-

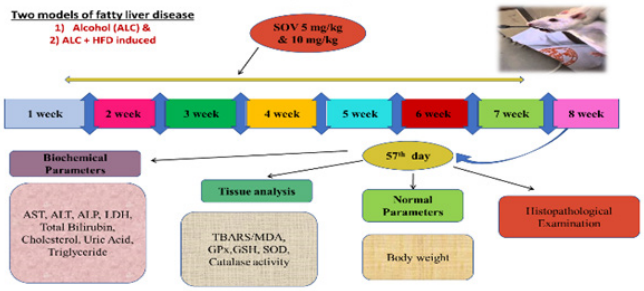

Fig. 1. Working model to study the effects of SOV on ALC and ALC + HFD-induced fatty liver disease models. Rats were subjected to **ALC and ALC + HFD** for 8 weeks to induce fatty liver disease. SOV was administered at the doses of 5 mg/kg and 10 mg/kg body weight in both models throughout the study period. After 8 weeks, blood and liver tissues were collected for analysis. Liver toxicity parameters were assessed from serum, while antioxidant parameters were measured from liver tissue lysates. Histopathological examination of liver sections was performed to evaluate morphological changes associated with liver damage and the potential protective effects of SOV.

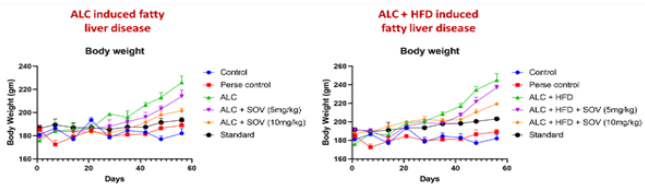

Fig. 2. Effect of SOV (5 and 10 mg/kg) pre-treatment on mean body weight. After the rat was stabilised, its body weight (g) was measured using a digital animal weighing equipment. On the first day (before treatments) and every week after that (weeks 1, 2, 3, 4, 5, 6, 7, and 8) the mean body weights of each group were measured. The control group's mean body weight gradually increased. In both the ALC and ALC + HFD-induced models, rats body weights are considerably reduced by pre-treatment with SOV. One-way ANOVA was used for analysis, and all values were displayed as mean ± SD (n = 6).

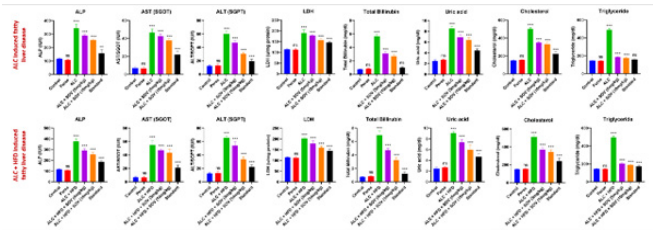

Fig. 3. Assessment of metabolic and liver function parameters in rat serum. Blood was collected before sacrificing animals of both models (ALC & ALC + HFD) and was subjected to determine the metabolic as well as liver biomarkers (ALP, AST, ALT, LDH, Total bilirubin, uric acid, cholesterol, and triglyceride). One-way ANOVA was used for analysis, and all values were displayed as mean ± SD (n = 6).

evated serum levels of ALP, AST (SGOT), ALT (SGPT), LDH, total bilirubin, uric acid, cholesterol, and triglycerides compared to the control group. SOV treatment (5 mg/kg and 10 mg/kg) dose-dependently reduced these biomarkers, with SOV (10 mg/kg) showing a more pronounced effect. The standard drug effectively mitigated these biochemical alterations, with an enhanced effect in comparison with SOV (10 mg/kg), which exhibited comparable efficacy to the standard drug. Similarly, in the ALC + HFD group, alcohol and high-fat diet consumption significantly increased serum biomarker levels, while SOV (5 mg/kg and 10 mg/kg) dose-dependently reduced these elevations, with SOV (10 mg/kg) showing greater efficacy. The standard drug demonstrated the most substantial reduction, especially when compared with SOV (10 mg/kg) (Fig. 3). Overall, the ALC group showed a more effective response in reducing serum biomarker levels than the ALC + HFD group, suggesting that alcohol alone may have a greater impact on biochemical changes, while the combination of alcohol and a high-fat diet may alter the metabolic response to treatment.

3.4. Anti-oxidant effect of SOV in ALC & ALC + HFD-Induced hepatotoxicity model

Alcohol exposure in the ALC group significantly increased hepatic TBARS levels while decreasing GPx, SOD, catalase, and GSH activity compared to the control group. SOV treatment (5 mg/kg and 10 mg/kg) dose-dependently reduced TBARS levels and mitigated alcohol-induced oxidative stress, with SOV (10 mg/kg) showing a more pronounced effect. Additionally, SOV treatment prevented the alcohol-triggered decline in SOD and GPx activity while significantly increasing catalase levels. The standard drug also effectively reduced oxidative stress, with SOV (10 mg/kg) displaying comparable efficacy. Similarly, in the ALC + HFD group, chronic alcohol and high-fat diet exposure significantly increased TBARS levels and decreased GPx, SOD, catalase, and GSH activity. SOV treatment dose-dependently reversed these changes, with SOV (10 mg/kg) being more effective. Compared to the standard drug, SOV (10 mg/kg) demonstrated a similar ability to reduce oxidative stress (Fig. 4). Overall, the ALC group showed a more effective response in reducing oxidative stress biomarkers than the ALC + HFD group, suggesting that alcohol alone exerts a greater influence on oxidative stress, while the combination of alcohol and a high-fat diet may alter the metabolic response to treatment.

3.5. Histopathological evaluation of liver tissues

Histological analysis of liver sections revealed distinct structural differences among the experimental groups. The control group exhibited normal hepatic architecture with well-preserved hepatocytes and sinusoidal structures. In contrast, rats exposed to alcohol (ALC) or alcohol + high-fat diet (ALC + HFD) showed significant hepatic damage, characterized by vacuolar and granular degeneration of hepatocytes, sinusoidal dilation, and widening of the portal triad (PT), as indicated by the presence of marked histopathological alterations. SOV treatment (10 mg/kg) for 8 weeks demonstrated a protective effect against ALC-induced liver injury than the 5 mg/kg dose. In the ALC model, SOV administration notably mitigated hepatic damage, with a marked reduction in portal triad widening and overall tissue degeneration. However, in the ALC + HFD model, although SOV treatment improved liver histology, the extent of portal triad widening remained more pronounced compared to the ALC-only group, suggesting a potentially greater challenge in reversing liver damage in

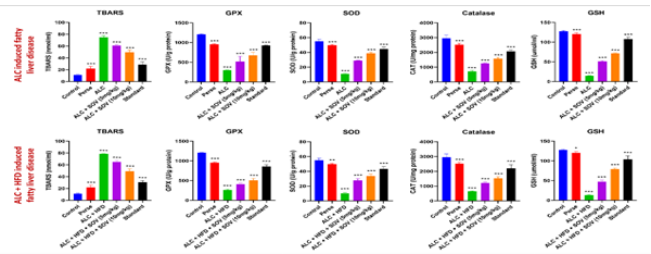

Fig. 4. Assessment of anti-oxidative effect of SOV in ALC and ALC + HFD induced FLD model. Effect of SOV (5 and 10 mg/kg) pre-treatment for 8 weeks on hepatic oxidative stress biomarkers in both ALC and ALC + HFD induced FLD model were measured by Thiobarbituric acid reactive substances (TBARS), reduced glutathione (GSH) content, superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) activity. Pre-treatment with SOV (5, and 10 mg/kg) significantly prevents hepatotoxicity by increasing TBARS content and decrease in GSH, SOD, CAT, and GPx activity in hepatic tissues lysate. All values were presented as mean ± SD (n = 6) and analysed using one-way ANOVA.

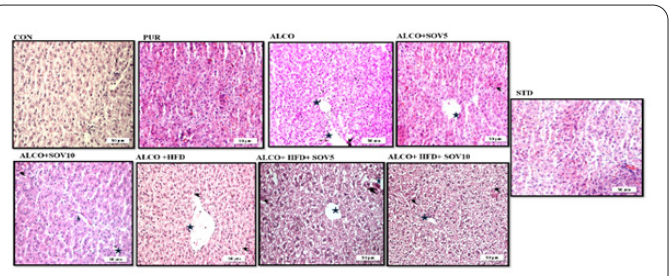

Fig. 5. Histopathological analysis of liver tissues following SOV treatment in alcohol- and alcohol + HFD-induced fatty liver disease models. The liver sections (5 µm) were stained with haematoxylin and eosin (H&E) after sacrifice and analysed using a light microscope. Representative liver sections from different experimental groups are shown. The control group exhibited a normal hepatic structure, while alcohol (ALC) and alcohol + high-fat diet (ALC + HFD) exposure led to vacuolar and granular degeneration, sinusoidal dilation, and widening of the portal triad (PT, marked by a star). Notably, SOV treatment (10 mg/kg) for 8 weeks alleviated liver damage, with a more pronounced reduction in portal triad widening observed in the ALC-induced model compared to the ALC + HFD model.

the presence of both ALC and ALC + HFD-induced metabolic stress (Fig. 5).

4. Discussion

Excessive lipid buildup in hepatocytes is a common hepatic problem known as FLD. It can lead to more serious disorders such as cirrhosis, fibrosis and hepatitis. It falls within the general category of alcoholic fatty liver disease, which is closely linked to obesity, insulin resistance, metabolic syndrome, and dyslipidaemia. Numerous intricate processes, such as oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, and inflammatory signalling, are involved in the pathophysiology of FLD. Because it can alter insulin signalling, lower oxidative stress, and enhance lipid metabolism. Sodium orthovanadate, a well-known phosphatase inhibitor, has been studied for possible hepatoprotective benefits. Developing focused treatment plans to stop the course of the disease requires an understanding of these pathways and the function of SOV. In this work, we assessed SOV potential as a treatment in two models of fatty liver disease: induced by ALC and ALC + HFD. Although its effectiveness was somewhat lower than that of the standard drug employed in this study. Our results show that administering SOV at a dose of 10 mg/kg body weight produced better hepato-protective effects than the 5 mg/kg dose. Significantly, SOV showed more effectiveness in the ALC-induced model as opposed to the ALC + HFD-induced model, suggesting that it may have a function in reducing liver damage brought on by ALC [19].

Body weight alterations imply that SOV therapy could aid in regulating the metabolic dysregulation linked to fatty liver disease. Improvements in liver function biomarkers such as total bilirubin, LDH, AST, ALT, and ALP show that SOV successfully lessens hepatic damage. Significant liver damage is shown by the increased levels of these enzymes in the untreated groups, but hepatoprotective benefits are suggested by their decrease after SOV treatment. Furthermore, SOV therapy markedly reduced metabolic indicators like triglycerides, cholesterol, and uric acid in ALC-induced model. These results imply that SOV might be involved in controlling lipid metabolism and avoiding the liver's overabundance of lipid buildup. However, the antioxidant potential of SOV is further supported by the results of the lipid peroxidation assay, which were determined by the TBARS/MDA levels. The decrease in oxidative stress indicators suggests that SOV aids in reducing lipid peroxidation, which is a major cause of liver damage in fatty liver disease. Additionally. The evaluation of the activity of antioxidant enzymes such as GPX, GSH, SOD, and catalase showed that SOV strengthens the liver's natural defences against oxidative stress. The potential of SOV to combat reactive oxygen species (ROS) and enhance redox equilibrium in hepatic tissues is indicated by the rise in these antioxidant indicators after SOV treatment. Furthermore, these biochemical results were confirmed by histopathological investigation employing haematoxylin and eosin (H&E) staining. The untreated group of liver sections showed substantial steatosis, inflammatory infiltration, and hepatocyte ballooning. On the other hand, especially in the ALC-induced model, SOV-treated groups demonstrated a notable improvement in hepatic architecture, with decreased steatosis and inflammation. However, the effects of SOV were substantially lessened in the ALC and HFD induced model, and together seemed to worsen liver damage. This implies that although SOV is useful in reducing liver damage brought on by alcohol, its effectiveness might be diminished when other metabolic stressors, such as HFD, are present. The various pathophysiological pathways behind ALC-induced and ALC + HFD-induced fatty liver disease may be the cause of the varied responses seen in the two animals. Oxidative stress and inflammation were caused by the harmful metabolites produced by ALC metabolism, including acetaldehyde and ROS. These effects seem to be adequately counteracted by SOV, but the additional burden, probably makes fat buildup, insulin resistance, and the generation of pro-inflammatory cytokines worse, leaving the liver more vulnerable to harm and possibly decreasing the effectiveness of SOV [20, 21].

Collectively, our research shows that SOV has promise as a treatment for fatty liver disease brought on by alcohol. Improvements in oxidative stress control, lipid metabolism, and liver function markers most likely mediate its hepatoprotective benefits. Although SOV exhibits promise, more investigation is required to clarify its exact molecular mechanisms and evaluate its long-term effectiveness when used in conjunction with dietary changes or other pharmaceutical medications to treat fatty liver disease.

Acknowledgments

None

Conflict of interest

There is no Conflict of Interest

Funding

None

Author contributions

Hema Rani (H.R.) conducted the experiments, collected and analyzed the data, and drafted the original manuscript. Anjana Devi (A.D.) conceptualized and designed the study, supervised the research work, and reviewed and edited the manuscript. Navdeep Singh (N.S.) contributed to methodology development, data interpretation, and critical revision of the manuscript. All authors have read and approved the final version of the manuscript.

Data availability statement

The datasets generated and analyzed during the current study are available from the the corresponding author upon reasonable request.

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