Systems Pharmacology-Based Elucidation of Sinapic Acid against High-Fat High-Fructose Diet-Induced Non-Alcoholic Fatty Liver Disease

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ABSTRACT

High-fat diet (HFD)-induced liver injury is a growing health concern due to its strong association with metabolic disorders and its progression to severe hepatic complications. Oxidative stress and inflammatory cell death mechanisms, particularly pyroptosis, play critical roles in its pathogenesis. Sinapic acid, a naturally occurring phenolic compound found in cereals, oilseeds, fruits, and vegetables, exhibits potent antioxidant and anti-inflammatory properties. The present study aimed to evaluate the hepatoprotective potential of sinapic acid against HFD-induced liver injury using an experimental rat model, complemented by an in silico network pharmacology approach to elucidate its molecular mechanisms. Hepatotoxicity was induced in Wistar albino rats through prolonged administration of an HFD. The protective effects of sinapic acid were assessed by analyzing serum biochemical markers, including SGOT, SGPT, ALP, total cholesterol, triglycerides, and HDL levels. Oxidative stress parameters such as reduced glutathione (GSH), malondialdehyde (MDA), catalase (CAT), and superoxide dismutase (SOD) were also evaluated. Histopathological examination of liver tissues was performed to assess structural and cellular alterations. Network pharmacology analysis identified multiple molecular targets of sinapic acid involved in oxidative stress regulation, lipid metabolism, and inflammatory signaling pathways, including apoptosis and pyroptosis-related mediators. Pathway enrichment analysis indicated significant modulation of NF-κB, MAPK, and antioxidant defense pathways. The findings demonstrated that sinapic acid significantly ameliorated biochemical and oxidative stress markers and preserved liver histoarchitecture in HFD-fed rats. These effects may be attributed to its multi-target mechanisms of action. Overall, the study suggests that sinapic acid holds promise as a therapeutic agent for managing diet-induced liver injury.

Key Words: Liver injury, Hepatotoxicity, Sinapic acid, Antioxidant, Pyroptosis and Network pharmacology.

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INTRODUCTION:

High-fat diet (HFD)-associated liver injury has emerged as a major global health concern due to its close association with obesity, insulin resistance, and metabolic syndrome. Chronic consumption of an HFD leads to excessive lipid accumulation in hepatocytes[1], resulting in hepatic steatosis, which can further progress to non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis. The rising prevalence of diet-induced liver disorders necessitates the development of effective preventive and therapeutic strategies [2, 3].

Oxidative stress plays a pivotal role in the progression of HFD-induced liver injury. Excess lipid accumulation enhances the production of reactive oxygen species (ROS), leading to disruption of cellular redox homeostasis, biomolecular damage, and activation of inflammatory responses [4]. Additionally, pyroptosis, a form of inflammatory programmed cell death mediated by inflammasomes such as NLRP3, has been identified as a key mechanism contributing to hepatic injury. Activation of pyroptotic pathways promotes the release of pro-inflammatory cytokines, including IL-1β and IL-18, thereby aggravating hepatic inflammation and disease progression [5, 6].

Natural compounds with antioxidant and anti-inflammatory properties have gained considerable attention for their hepatoprotective potential. Sinapic acid, a phenolic compound abundantly present in cereals, oilseeds, fruits, and vegetables, exhibits potent antioxidant, anti-inflammatory, and free radical scavenging activities. Despite its promising

pharmacological properties, its role in mitigating HFD-induced liver injury, particularly via modulation of oxidative stress and pyroptosis, remains inadequately explored [7-9].

The present study aimed to evaluate the hepatoprotective effect of sinapic acid against HFD-induced hepatotoxicity in Wistar rats. Biochemical parameters, lipid profile, body and liver weight, and histopathological changes were assessed to determine its protective efficacy. The findings provide comprehensive insights into the therapeutic potential of sinapic acid in managing diet-induced liver injury [10-12].

MATERIALS AND METHODS:

MATERIALS:

Experimental Animals:

Healthy male Wistar albino rats (6–8 weeks old) were procured from LACSMI BioFarms (Laboratory Animal Centre for Safe Medical Innovations), Pune, Maharashtra, India (CCSEA Registration No.: 1277/PO/RcBt/S/09/CCSEA). The animals were housed in the animal facility of MET's BKC Institute of Pharmacy in polypropylene cages containing clean rice husk bedding. Standard laboratory conditions were maintained, including a temperature of 25 ± 2 °C, relative humidity of 55 ± 5%, and a 12-hour light/dark cycle. The animals had free access to standard pellet diet and potable water ad libitum.

All experimental protocols were reviewed and approved by the Institutional Animal Ethics Committee (IAEC) of MET's BKC Institute of Pharmacy (Approval No.: MET-IOP-IAEC/2024-25/04). The study was conducted in strict accordance with the guidelines prescribed by the Committee for Control and Supervision of Experiments on Animals (CCSEA).

Chemicals and Reagents:

Sinapic acid was procured from P.C. Chem India. Biochemical estimations were carried out using commercially available diagnostic kits for aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total cholesterol (TC), low-density lipoprotein (LDL), triglycerides (TG), and high-density lipoprotein (HDL), obtained from AutoMAX 200. Ellman's reagent was purchased from Ottokemi, while Tris hydrochloride (Tris-HCl) was procured from Research Lab Fine Chem Industries. Trichloroacetic acid (TCA) and thiobarbituric acid (TBA) were obtained from Loba Chemie Pvt. Ltd. All chemicals and reagents used in the study were of analytical grade. Biochemical analyses were performed using an automated bioanalyzer. Sample separation was carried out using a Remi centrifuge, and all volumetric measurements were conducted using calibrated micropipettes to ensure accuracy and reproducibility.

METHODS:

Target Identification and Network Pharmacology Analysis:

Potential molecular targets of sinapic acid were identified using the PubChem database. Further target prediction was performed using the SwissTargetPrediction platform by selecting *Homo sapiens* as the target organism. The canonical SMILES structure of sinapic acid was submitted, and predicted targets with a probability greater than 0.10 were selected for further analysis. The identified targets were compiled and utilized for subsequent network pharmacology and pathway enrichment studies associated with non-alcoholic fatty liver disease (NAFLD) [13, 14].

Protein–Protein Interaction (PPI) Network Construction and Analysis:

Protein–protein interaction (PPI) networks were constructed and analyzed using Cytoscape software. The STRING database was employed to evaluate interactions among overlapping targets of sinapic acid and NAFLD, facilitating the identification of hub genes and functional associations based on interaction confidence scores. Topological analysis of the PPI network was conducted to determine key hub targets. Additionally, DAVID was used for Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis to elucidate the biological processes and signaling pathways underlying the hepatoprotective effects of sinapic acid [15, 16].

Animals and Treatment Protocol:

After a one-week acclimatization period, the animals were randomly allocated into experimental groups. A total of 36 rats were used in the study. Initially, rats were divided into two groups: a normal control group (n = 6), which received a normal pellet diet (NPD), and a high-fat high-fructose (HFHF) diet group (n = 30), which was fed for 5 consecutive weeks to induce metabolic and hepatic alterations. The composition of the HFHF diet is presented in Table 1. The normal pellet diet (NPD) comprised 65% carbohydrates, 3% fat, 18% crude protein, 5% vitamins and minerals, and 6% crude fiber [17-19]. The composition and preparation of HFHF diet are mentioned in [Table 1].

Table 1: Composition of high-fat- high fructose diet

Sr. No.	Ingredient	Diet (g/100 g)
1	Powdered NPD*	37.0
2	Vegetable ghee *(44% palmitic acid, 5% stearic acid, 39% oleic acid, 10% linoleic acid)*	25.0
3	Casein	10.0
4	Fructose	20.0
5	Cholesterol	5.0
6	Vitamin and Mineral Mix	3.0
7	Others	--
8	Total	100 g

*The composition of NPD (normal pellet diet): 65% carbohydrates, 3% fat, 18% crude protein, 5% vitamins and minerals, and 6% crude fiber

From the beginning of the 6th week, HFHF-fed animals were further divided into five groups (n = 6 each), while the normal control group continued on the standard diet. Thus, a total of six groups were maintained from weeks 6 to 10. The grouping and treatment protocol were as follows:

- **Group I (Normal Control):** Received normal pellet diet and vehicle for 10 weeks.
- **Group II (Disease Control):** Received HFHF diet throughout the experimental period.
- **Group III (Standard):** Received HFHF diet and silymarin (50 mg/kg, p.o.).
- **Group IV (Low Dose):** Received HFHF diet and sinapic acid (40 mg/kg, p.o.).
- **Group V (Medium Dose):** Received HFHF diet and sinapic acid (80 mg/kg, p.o.).
- **Group VI (High Dose):** Received HFHF diet and sinapic acid (100 mg/kg, p.o.).

All treatments were administered orally once daily from week 6 to week 10.

At the end of the experimental period, animals were anesthetized under light chloroform anesthesia. Blood samples were collected via tail vein puncture for biochemical analysis. Parameters assessed included body weight, liver weight, total cholesterol, triglycerides (TAG), lactate dehydrogenase (LDH), serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, and total protein. The animals were sacrificed by cervical dislocation, and liver tissues were excised, weighed, and subjected to histopathological examination. Additionally, oxidative stress markers and biochemical parameters were evaluated to determine the hepatoprotective effects of the treatments on liver function and morphology [20-22].

Histopathological Observation:

Liver tissues were fixed in 10% formalin for 24 hours at room temperature. The fixed tissues were then processed, embedded in paraffin, and sectioned into thin slices of approximately 5 µm thickness. The sections were stained with hematoxylin and eosin (H&E) and examined under a light microscope at 20× magnification for histopathological evaluation [23, 24].

Statistical Analysis:

All experimental data were expressed as mean ± standard error of the mean (SEM). Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison test to determine the significance of differences between groups. A value of $p < 0.05$ was considered statistically significant. Analysis was carried out using GraphPad Prism version 9 software [25, 26].

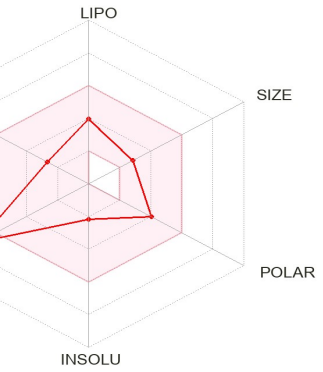
RESULTS:

Phytochemical Screening and Network Pharmacology Analysis:

Sinapic acid (purity ≥ 98%) was procured from a certified commercial source. As a single, well-characterized phytoconstituent was employed in the present study, preliminary phytochemical screening was not performed. The identity and purity of the compound were confirmed based on the supplier's certificate of analysis and its established physicochemical properties. To elucidate the molecular mechanisms underlying the hepatoprotective effects of sinapic acid, a network pharmacology approach was employed. Potential molecular targets of sinapic acid were predicted using publicly available databases and subsequently intersected with hepatotoxicity- and non-alcoholic fatty liver disease (NAFLD)-associated targets to identify key therapeutic candidates.

The bioavailability radar plot (Figure 1a), generated using SwissADME, provides an overview of the drug-likeness profile of sinapic acid based on six key physicochemical parameters: lipophilicity, molecular size, polarity, solubility, flexibility, and saturation. The compound was observed to fall predominantly within the optimal range (pink region), indicating a favorable balance of physicochemical properties for oral bioavailability. Parameters such as lipophilicity and molecular size were within acceptable limits, supporting membrane permeability, while polarity and

solubility suggested good absorption characteristics with limited molecular flexibility.



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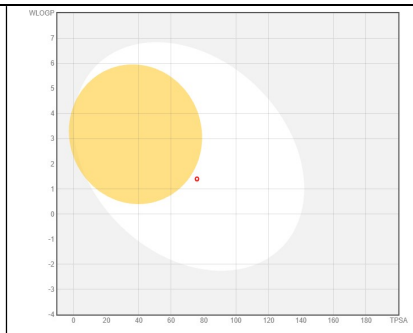

Figure 2b The BOILED-Egg model

The BOILED-Egg model (Figure 1b) further predicted the pharmacokinetic behavior of sinapic acid in terms of gastrointestinal absorption and blood–brain barrier (BBB) permeability. The compound was positioned within the white region, indicating a high probability of passive intestinal absorption. However, its exclusion from the yolk region suggests limited BBB permeability, indicating minimal central nervous system exposure. This pharmacokinetic profile supports its suitability as an orally active hepatoprotective agent.

Network pharmacology analysis identified 132 potential targets of sinapic acid using SwissTargetPrediction, while 1,248 NAFLD-associated genes were retrieved from GeneCards and OMIM databases. Comparative analysis revealed 48 overlapping targets, suggesting a potential therapeutic association between sinapic acid and NAFLD.

The compound–target network demonstrated that sinapic acid interacts with multiple proteins, indicating a multi-target mode of action. Protein–protein interaction (PPI) network analysis further identified key hub genes, including TNF, IL6, AKT1, and CASP3, which are critically involved in inflammation, apoptosis, and cell survival pathways.

Gene Ontology (GO) enrichment analysis indicated that the overlapping targets were primarily associated with biological processes such as lipid metabolism, inflammatory response, oxidative stress, and apoptosis. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis revealed significant enrichment in pathways such as PI3K–Akt, MAPK, TNF, and PPAR signaling, along with pathways related to insulin resistance and AGE–RAGE signaling.

Biochemical Estimation:

The effect of sinapic acid on liver function markers and lipid profile parameters in high-fat diet-induced hepatic injury is presented in Figures 2 and 3. After 10 weeks of experimental treatment, biochemical analysis demonstrated a significant ($P < 0.05$) elevation in hepatic enzyme levels, including alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), and alkaline phosphatase (ALP) in the disease control group compared to the normal control group, indicating hepatocellular damage and compromised liver integrity. Similarly, lipid profile parameters such as total cholesterol (TC), low-density lipoprotein (LDL), triglycerides (TG), and very low-density lipoprotein (VLDL) were significantly increased, whereas high-density lipoprotein (HDL) levels were markedly decreased, reflecting dyslipidemia associated with high-fat diet-induced metabolic disturbances (Figure 2a-c)..

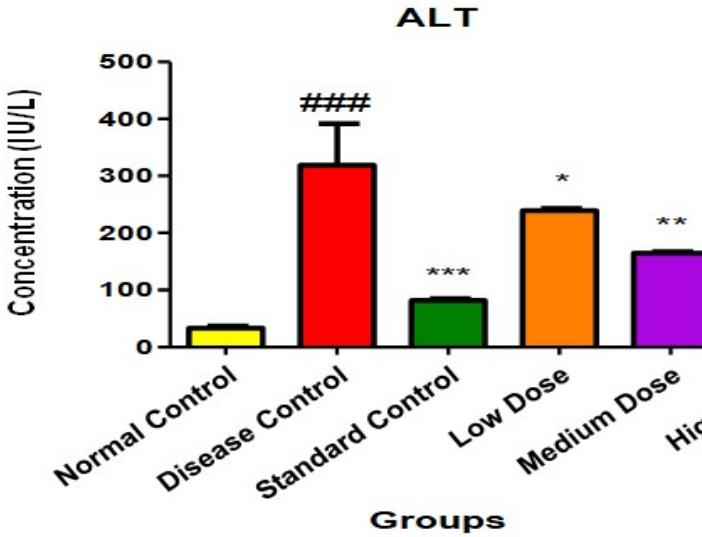

Figure 2a: Effect of Sinapic acid (40,80and100mg/kg po.) on ALT/SGPT level (IU/L)

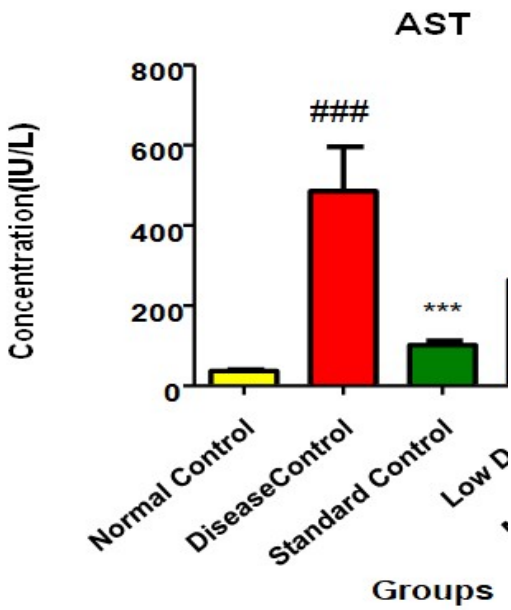

Figure 2b: Effect of Sinapic acid (40,80and100mg/kgp.o.) on level of AST/SGOT (IU/L)

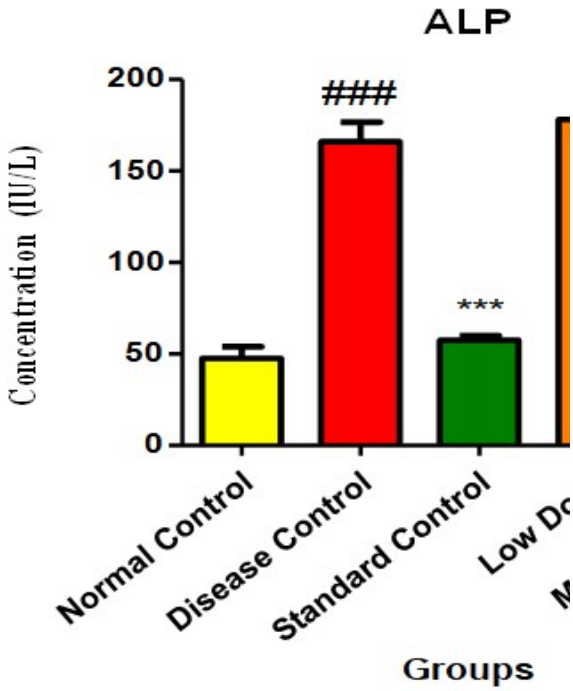

Figure 2c: Effect of Sinapic acid (40,80and100mg/kgp.o.) on level of ALP (IU/L)

Treatment with sinapic acid at doses of 40, 80, and 100 mg/kg p.o. resulted in a dose-dependent reduction in liver enzyme levels. Notably, significant decreases in ALT and AST levels were observed in the 80 and 100 mg/kg treated groups compared to the disease control group, suggesting hepatoprotective activity of sinapic acid. The highest dose (100 mg/kg) showed maximum restoration of enzyme levels toward normal values, comparable to the standard drug-treated group. The reduction in ALP levels further indicates improvement in biliary function and membrane stability (Figure 3a-d).

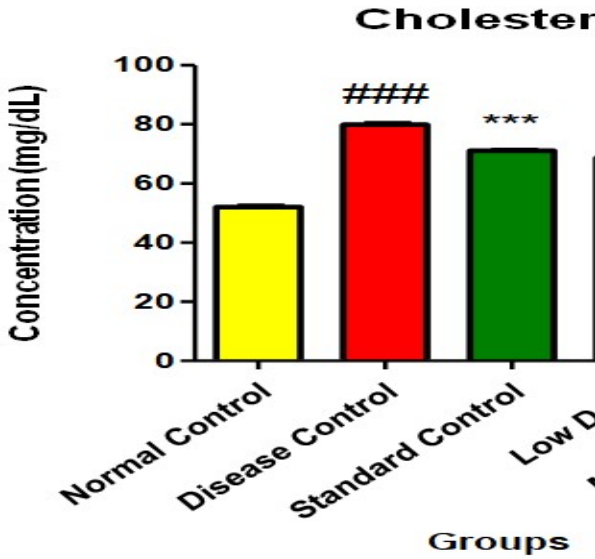

Figure 3a: Effect of Sinapic acid (40,80 and 100mg/kgp.o.)on level of Cholesterol (mg/dL)

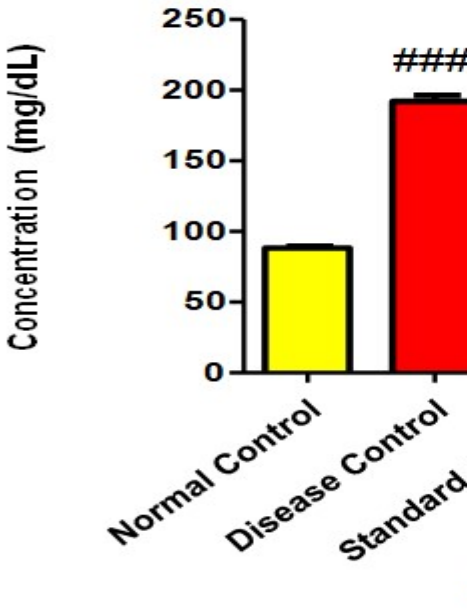

Figure3b: Effect of Sinapic acid(40,80and100mg/kgp.o.) on level of low-density lipoprotein (mg/dL)

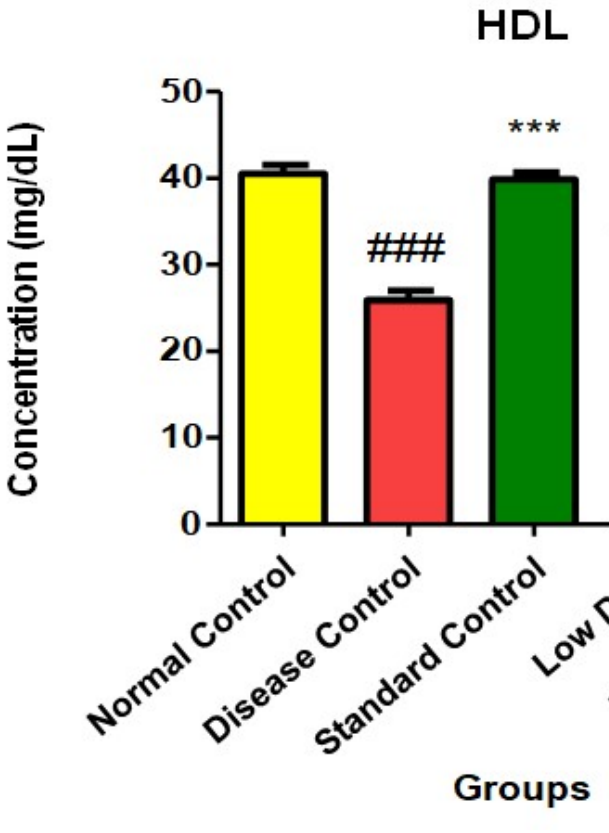

Figure 3d: Effect of Sinapic acid (40,80and100mg/kgp.o.) On level of HDL (mg/dL)

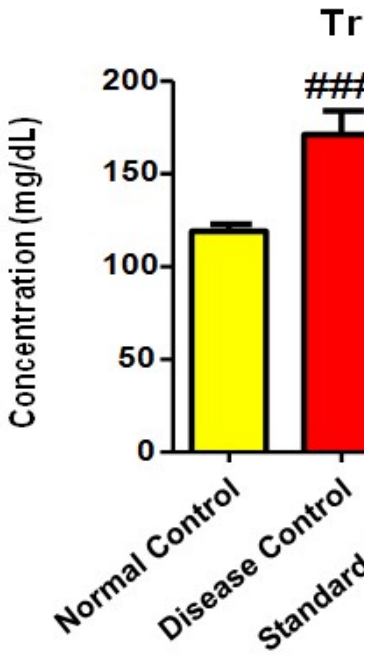

Figure 3c: Effect of Sinapic acid (40,80and100mg/kgp.o.) On level of Triglyceride (mg/dL)

Regarding lipid profile parameters, sinapic acid treatment exhibited significant improvement at moderate and higher doses (80 and 100 mg/kg). These groups showed a marked reduction in total cholesterol, LDL, triglycerides, and VLDL levels compared to the disease control group. However, the lowest dose (40 mg/kg) did not produce statistically significant changes in most lipid parameters, indicating that a threshold dose is required to exert hypolipidemic effects.

Furthermore, HDL levels were significantly increased in the 80 and 100 mg/kg treated groups, suggesting enhanced reverse cholesterol transport and cardioprotective potential. The improvement in lipid profile may be attributed to the antioxidant and lipid-lowering properties of sinapic acid, which help in reducing oxidative stress and regulating lipid metabolism.

These findings indicate that sinapic acid possesses significant hepatoprotective and antihyperlipidemic effects in a dose-dependent manner. The observed biochemical improvements suggest that sinapic acid

mitigates hepatic injury by stabilizing hepatocyte membranes, reducing enzyme leakage, and improving lipid homeostasis under high-fat diet-induced pathological conditions.

Estimation of Oxidative Stress Markers:
The effect of sinapic acid on oxidative stress parameters in high-fat diet-induced hepatic injury is illustrated in Figure 4. Oxidative stress plays a critical role in the progression of liver damage, primarily through the generation of reactive oxygen species (ROS), which impair cellular antioxidant defense systems. In the present study, the disease control group exhibited a significant ($P < 0.05$) decrease in endogenous antioxidant markers, including reduced glutathione (GSH), catalase (CAT), and superoxide dismutase (SOD), along with a significant increase in lipid peroxidation (LPO) levels compared to the normal control group. The elevated LPO levels indicate enhanced oxidative degradation of lipids, leading to membrane damage, while reduced levels of GSH, CAT, and SOD reflect compromised antioxidant defense mechanisms. Oxidative stress parameters were evaluated to assess the antioxidant potential of sinapic acid in HFHF diet-induced hepatic injury (Figure 4a-d).

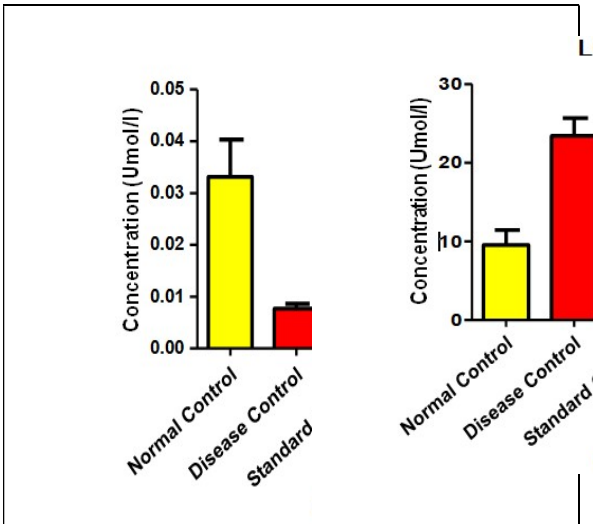

Figure 4a :Effect of Sinapic acid (40, 80 and 100 mg/kg p.o.) on level of reduced glutathione	Figure 4 b: Effect of Sinapic acid (40, 80 and 100 mg/kg p.o.) on lipid Per oxidation

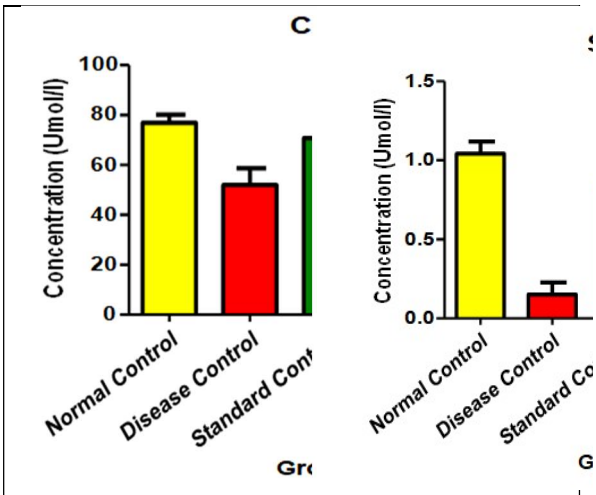

Figure 4c: Effect of Sinapic acid(40, 80and100mg/kgp.o.)on catalase	Figure 4d: Effect of Sinapic acid (40, 80and100mg/kgp.o.)on superoxide dismutase

Reduced Glutathione (GSH):
A significant depletion of reduced glutathione (GSH) levels was observed in the disease control group, indicating exhaustion of endogenous antioxidant reserves due to excessive free radical generation. Treatment with sinapic acid (40, 80, and 100 mg/kg, p.o.) resulted in a dose-dependent restoration of GSH levels. Notably, the higher doses (80 and 100 mg/kg) produced effects comparable to the standard drug silymarin (50 mg/kg), suggesting effective recovery of intracellular redox balance and antioxidant defense (Figure 4a).

Lipid Peroxidation (LPO)/Malondialdehyde (MDA):
Malondialdehyde (MDA), a key biomarker of lipid peroxidation, was significantly elevated in HFHF-fed rats, reflecting enhanced oxidative damage to cellular membranes. Administration of sinapic acid markedly reduced MDA levels in a dose-dependent manner. The higher doses (80 and 100 mg/kg) demonstrated pronounced inhibition of lipid peroxidation, comparable to silymarin, whereas the lower dose (40 mg/kg) showed only a moderate effect (Figure 4b).

Catalase (CAT):
Catalase (CAT) activity was significantly decreased in the disease control group, indicating impaired detoxification of hydrogen peroxide and increased oxidative burden. Treatment with sinapic acid significantly enhanced CAT activity, particularly at 80

and 100 mg/kg doses, where the enzyme levels approached normal control values and were comparable to those observed in the silymarin-treated group (Figure 4c).

Superoxide Dismutase (SOD):
Superoxide dismutase (SOD) activity was also markedly reduced following HFHF exposure, reflecting weakened primary antioxidant defense against superoxide radicals. Sinapic acid administration resulted in a significant, dose-dependent increase in SOD activity. The higher doses (80 and 100 mg/kg) showed substantial restoration, closely matching the effects of the standard drug silymarin (Figure 4d).

Histopathological Assessment of Liver Tissue:
Histopathological evaluation of liver sections provided further confirmation of the hepatoprotective effect of sinapic acid against HFHF diet-induced hepatic injury (Figure 5). Liver sections from the normal control group (Figure 5a) exhibited normal hepatic architecture, characterized by well-arranged hepatocytes with clear cytoplasm, intact cell boundaries, and centrally located nuclei. The central vein and surrounding sinusoidal spaces appeared normal, indicating the absence of any pathological alterations. In contrast, liver sections from the disease control group (HFHF diet-fed rats) (Figure 5b) showed significant histopathological abnormalities. These included pronounced fatty degeneration of hepatocytes, with both microvesicular and macrovesicular lipid accumulation, confirming the development of hepatic steatosis. Additionally, distortion of hepatic architecture and hepatocellular ballooning were evident, indicating severe liver injury. Treatment with sinapic acid at doses of 40 and 80 mg/kg p.o. (Figures 5c and 5d) resulted in moderate improvement in liver histology. These groups showed a reduction in lipid accumulation and fewer microvesicular fat droplets compared to the disease control group. However, mild fatty changes and partial disruption of hepatic architecture were still observed, suggesting incomplete protection at these doses.

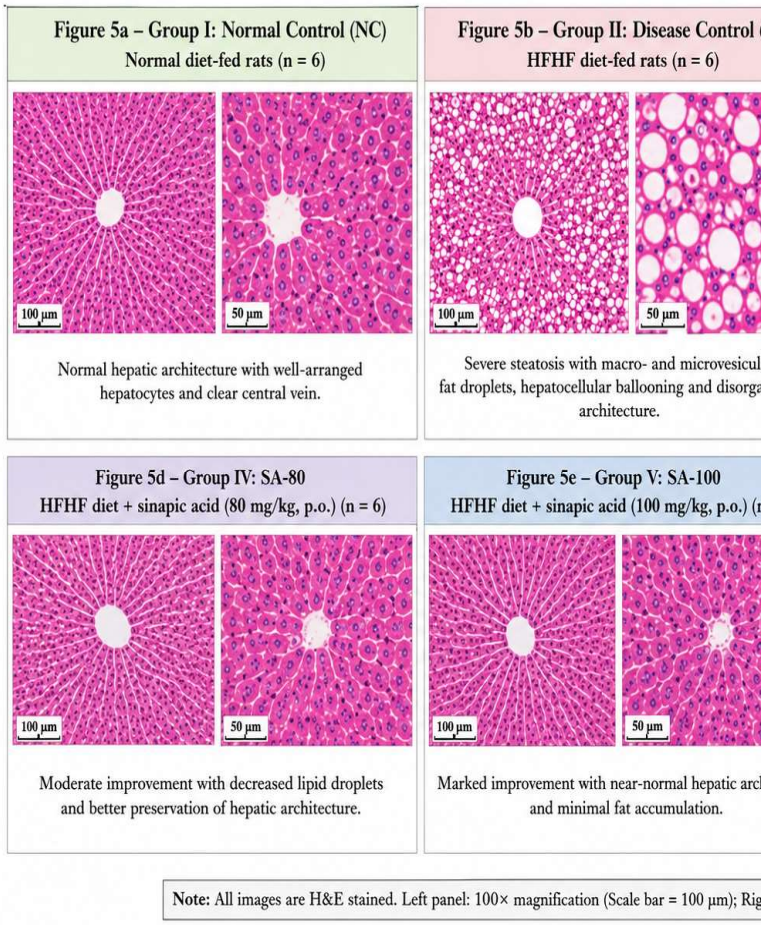

Figure 5: Histopathological analysis of liver sections (H&E staining) showing normal architecture in control (5a), severe steatosis in disease control (5b), mild to moderate improvement with sinapic acid at 40 and 80 mg/kg (5c–5d), marked restoration at 100 mg/kg (5e), and near-normal structure in silymarin-treated group (5f). Magnification: 100× (left), 400× (right).

Notably, liver sections from rats treated with sinapic acid at 100 mg/kg p.o. (Figure 5e) demonstrated marked restoration of normal hepatic structure. The hepatocytes appeared largely intact with minimal lipid deposition, reduced cellular degeneration, and improved sinusoidal arrangement. The overall architecture was comparable to that of the normal control group, indicating substantial hepatoprotection. Similarly, the standard drug-treated group receiving silymarin (50 mg/kg) (Figure 5f) exhibited near-normal liver histology, with well-preserved hepatocytes and negligible evidence of steatosis or cellular damage. These findings indicate that sinapic acid effectively ameliorates HFHF-induced hepatic

damage in a dose-dependent manner. The highest dose (100 mg/kg) demonstrated optimal hepatoprotective activity, comparable to the standard drug silymarin. The observed histological improvements corroborate the biochemical and antioxidant findings, suggesting that sinapic acid exerts its protective effects by reducing lipid accumulation, preventing cellular degeneration, and preserving hepatic architecture.

DISCUSSION:

High-fat high-fructose (HFHF) diet-induced liver injury is widely recognized as a major contributor to the development of non-alcoholic fatty liver disease (NAFLD), characterized by lipid accumulation, oxidative stress, inflammation, and progressive hepatic damage. The present study comprehensively evaluated the hepatoprotective potential of sinapic acid using biochemical, antioxidant, histopathological, and network pharmacology approaches [27].

In the current investigation, HFHF-fed rats exhibited significant elevations in serum hepatic enzymes (ALT, AST, and ALP), indicating hepatocellular injury and increased membrane permeability. These findings are consistent with previous reports demonstrating that lipid accumulation and oxidative stress disrupt hepatocyte integrity and promote enzyme leakage into circulation [28]. Treatment with sinapic acid resulted in a significant, dose-dependent reduction in these enzyme levels, suggesting stabilization of hepatocyte membranes and restoration of liver function. The effect observed at higher doses (80 and 100 mg/kg) was comparable to that of the standard drug silymarin, highlighting its potent hepatoprotective activity [29].

Dyslipidemia is a hallmark of NAFLD, and the HFHF diet significantly elevated total cholesterol, LDL, triglycerides, and VLDL levels while reducing HDL levels in the disease control group. Sinapic acid treatment effectively improved lipid profile parameters, particularly at moderate and higher doses. The reduction in atherogenic lipids and elevation of HDL suggests enhanced lipid metabolism and reverse cholesterol transport. These effects may be attributed to modulation of lipid regulatory pathways, as supported by network pharmacology findings indicating involvement of PPAR and PI3K–Akt signaling pathways [30,31].

Oxidative stress plays a central role in the pathogenesis of NAFLD by generating reactive oxygen species (ROS), which damage lipids, proteins, and DNA. In the present study, HFHF-fed rats showed increased lipid peroxidation (MDA) and decreased antioxidant defenses (GSH, CAT, and SOD), confirming oxidative imbalance. Administration of sinapic acid significantly restored antioxidant enzyme levels and reduced lipid peroxidation in a dose-dependent manner. The phenolic structure of sinapic acid enables efficient free radical scavenging and enhancement of endogenous antioxidant systems, thereby protecting hepatocytes from oxidative injury. These findings are in agreement with earlier reports highlighting the antioxidant potential of sinapic acid [32, 33].

Histopathological observations further substantiated the biochemical and oxidative findings. The disease control group exhibited severe hepatic steatosis, hepatocellular ballooning, and architectural distortion, whereas sinapic acid treatment markedly improved liver histology. The highest dose (100 mg/kg) demonstrated near-normal hepatic architecture with minimal lipid accumulation, comparable to the silymarin-treated group. This structural restoration confirms the ability of sinapic acid to prevent lipid deposition and cellular degeneration in hepatocytes [34].

Importantly, the network pharmacology analysis provided mechanistic insights into the multi-target action of sinapic acid. Key targets such as TNF, IL-6, AKT1, and CASP3 were identified, indicating its role in regulating inflammation, apoptosis, and cell survival pathways. Enrichment analysis revealed significant involvement of NF-κB, MAPK, and PI3K–Akt signaling pathways, which are known to mediate oxidative stress and inflammatory responses in NAFLD. Additionally, modulation of pyroptosis-related pathways suggests that sinapic acid may inhibit inflammatory cell death, thereby reducing hepatic injury [35].

In the present study demonstrates that sinapic acid exerts significant hepatoprotective effects through a multi-faceted mechanism involving antioxidant defense enhancement, lipid metabolism regulation, and suppression of inflammatory and apoptotic pathways. The dose-dependent efficacy observed across biochemical, oxidative, and histological parameters highlights its therapeutic potential. These findings suggest that sinapic acid may serve as a promising natural agent for the management of HFHF-induced liver injury and related metabolic disorders. However, further studies are warranted to elucidate its molecular mechanisms in detail and to validate its clinical applicability [36, 37].

CONCLUSION:

The present study demonstrates that sinapic acid possesses significant hepatoprotective potential against high-fat high-fructose (HFHF) diet-induced liver injury. Administration of sinapic acid effectively improved biochemical markers of liver function, restored lipid profile balance, and enhanced

endogenous antioxidant defense systems, as evidenced by increased levels of GSH, CAT, and SOD along with reduced lipid peroxidation. Histopathological findings further confirmed its protective role by showing marked restoration of hepatic architecture and reduction in steatosis, particularly at higher doses. The hepatoprotective effects of sinapic acid appear to be mediated through its antioxidant, antihyperlipidemic, and anti-inflammatory properties, supported by network pharmacology analysis indicating modulation of key signaling pathways involved in oxidative stress, inflammation, and apoptosis. Sinapic acid exhibited dose-dependent efficacy, with the 100 mg/kg dose showing effects comparable to the standard drug silymarin. These findings suggest that sinapic acid may serve as a promising natural therapeutic agent for the management of diet-induced liver injury and related metabolic disorders. Further studies are warranted to explore its detailed molecular mechanisms and clinical applicability.

Conflict of Interest:
None
Funding:
None

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