Lycopene Mitigates Sertraline-Triggered Hepatotoxicity: Modulation of Oxidative Stress and Liver Enzymes

Running title: Lycopene on Sertraline Hepatotoxicity

Ayla Sadeghzadeh[1], Hossein Kargar Jahromi[2], Enayatollah Bahman Jahromi[1*]

1- Department of chemistry, Ja.C., Islamic Azad University, Jahrom, Iran.

2- Department of Research Center for Noncommunicable Diseases, Jahrom University of Medical Sciences, Jahrom, Iran.

Corresponding Author: Enayatollah Bahman Jahromi, PhD of Organic Chemistry, Department of chemistry, Ja.C., Islamic Azad University, Jahrom, Iran. Postal Adress: Rahbari Avenue, Islamic Azad University, Jahrom, Iran, zip code: 7414785318, Email: bahmani871@iau.ac.ir , Oicid: 0000-0003-2425-5588

Abstract:

Introduction: Disruption of liver function can destabilize systemic biochemical balance, and drug-induced oxidative stress (OS) is the main factor in its induction. Sertraline may impair hepatic function by altering serotonin dynamics and interfering with enzymatic regulation. Lycopene, as a potent lipophilic antioxidant, counteracts these effects by scavenging free radicals and OS. The aim of this study is to investigate the hepatoprotective effects of lycopene in reducing sertraline-induced hepatotoxicity, focusing on OS parameters and liver-specific enzymes.

Material and Methods: Forty-eight male Wistar rats were randomly divided into six groups; they were treated for 28 days via oral gavage with sertraline alone or in combination with different doses of lycopene (12.5, 25, and 50 mg/kg). Biochemical analyses were performed on serum samples to assess AST, ALT, ALP, total bilirubin, malondialdehyde, and total antioxidant capacity (TAC). Statistical analysis was determined using by Tukey's post hoc test.

Results: Sertraline administration significantly increased serum concentrations of ALT, AST, ALP, malondialdehyde, and total bilirubin ($p<0.001$ for all ANOVA comparisons). Sertraline also reduced TAC ($p<0.001$). Concomitant treatment with lycopene, especially 50 mg/kg, significantly reversed these changes. This treatment reduced liver enzymes and OS markers (Malondialdehyde, TAC) and

restoring TAC ($p<0.001$). Lycopene hepatoprotective effect was dose-dependent and its greatest effect at the highest concentration.

Conclusion: Lycopene showed a dose-dependent protective effect against sertraline-induced hepatotoxicity by reducing OS and improving key biochemical markers. The 50 mg/kg dose had the greatest benefit, indicating its therapeutic adjunct. These results highlight the antioxidant efficacy of lycopene and support further research into its mechanistic pathways, pharmacodynamics, and long-term safety in drug-induced liver injury models.

Keywords: Antioxidant capacity, Liver enzymes, Lycopene, Oxidative stress, Sertraline.

1.Introduction

The liver serves as a organ in maintaining the body's biochemical balance and coordinates essential functions such as nutrient metabolism, glycogen storage, protein synthesis, detoxification, bile secretion, and urea production, all of which are vital for survival (1). Hepatic injury, whether acute or chronic, is usually reflected by increased serum biomarkers including Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP), and Alanine Aminotransferase (ALT) indicating liver cell damage and impaired liver function (2, 3). Other indicators such as increased levels of total bilirubin and Malondialdehyde (MDA), along with decreased total antioxidant capacity (TAC), highlight the presence of enzymes and OS markers, including malondialdehyde (MDA) as an index of lipid peroxidation and total antioxidant capacity (TAC) as a measure of systemic redox defense, serve as key parameters in the diagnosis and monitoring of liver damage. Furthermore, decreased total protein and serum albumin may indicate impaired synthesis function and take role in the clinical assessment of liver status (2). OS, driven by the accumulation of reactive oxygen species (ROS), remains one of the main mechanisms of liver cell injury. MDA, a lipid peroxidation product, is widely recognized as a sensitive biomarker for oxidative damage. TAC provides an integrated measure of the body's antioxidant defense ability against ROS-induced hepatotoxicity (4).

Sertraline could be a broadly endorsed antidepressant having a place to the specific serotonin reuptake inhibitor (SSRI) course, and is frequently used to manage depression and anxiety-related disorders. Despite its therapeutic benefits, accumulating evidence suggests that sertraline may elicit adverse effects, such as increased OS, sexual dysfunction, headaches, increased appetite and body weight, and even liver damage. Its hepatotoxic potential is thought to stem from impaired antioxidant defense mechanisms, increasing the production of ROS, and resulting in inflammatory cascades and histopathological changes in liver tissue, especially at high doses and long-term use (5, 6). While the psychiatric efficacy of sertraline is well established, the risk of liver injury associated with sertraline underscores the importance of identifying protective interventions.

In light of sertraline's hepatotoxic potential, lycopene ($C_{40}H_{56}$) has emerged as a promising protective agent. Lycopene is a naturally occurring carotenoid richly present in red fruits and tomatoes. This composition is lipophilic and shows powerful antioxidant and anti-inflammatory action, and can play an important role in reducing the damaging effects of OS and inflammation. It neutralizes ROS, inhibits lipid peroxidation, and has shown protective effects in various models of hepatotoxicity. By scavenging free radicals and attenuating lipid peroxidation, lycopene helps preserve hepatocyte integrity and mitigate drug-induced liver injury (7, 8). Lycopene able to reduce liver enzyme elevations and maintain tissue integrity after exposure to hepatotoxic agents, including chemotherapy, environmental toxins, and metabolic insults (9).

This project aimed to evaluate the hepatoprotective effect of lycopene on sertraline-induced liver injury, using a controlled rat model. The findings may inform the development of adjunctive antioxidant strategies to safeguard hepatic function in individuals undergoing prolonged antidepressant therapy. These findings may help develop adjunctive antioxidant strategies to preserve liver function in patients undergoing long-term treatment with antidepressants. By elucidating the protective mechanisms of lycopene, this research could provide preclinical evidence supporting its role in reducing liver damage and improving biochemical outcomes in drug-induced hepatotoxicity.

2. Materials and Methods

2.1. Ethical Approval

Experimental protocols adhered to institutional standards for animal welfare and received formal approval from the Ethics Committee of Jahrom University of Medical Sciences (IR.JUMS.AEC.1403.009).

2.1. Study Design and Study Animals

Forty-eight healthy male Wistar rats weighing 180 to 200 grams and aged 9 to 10 weeks were prepared. Rats were housed under standardized conditions(10), including a 12-hour dark/light cycle, ambient temperature of 23 ± 2°C, and relative humidity maintained at 55%. The doses of and lycopene were determined based on previous studies (11). Lycopen powder and sertraline purchased from Merck company (Germany). The animals randomly, using simple randomization, divided into 6 groups ($n = 8$/group): the control group, animals received no treatment; the sham group received normal saline and olive oil (vehicle) via gavage; the sertraline group received sertraline (0.5 mg/kg/day, oral gavage); Sertraline + Lycopene 12.5 mg/kg group, treated with sertraline and lycopene at a dose of 12.5 mg/kg per day; the sertraline + lycopene 25 mg/kg group was treated with sertraline and lycopene at a dose of 25 mg/kg per day, and the sertraline + lycopene 50 mg/kg group was treated with sertraline and lycopene at a dose of 50 mg/kg per day. Each group received its respective treatment once daily by oral gavage over a 28-day period. At the end of the experiment, the animals were weighed using a digital scale (0.01) (AND-EK610i- Japan).

2.3. Biochemical Analysis

At the end of the treatment period, rats were anesthetized using intraperitoneal ketamine (100 mg/kg) and xylazine (20 mg/kg) (Alfasan-Holland). Following cardiac puncture, blood samples were

centrifuged at 3000 rpm for 10 minutes (universal centrifuge- Sahand-Iran) to obtain serum. Serum samples were stored at −20 °C until analysis (12). Liver function markers including AST, ALT, ALP, total bilirubin, total protein (TP), and albumin (ALB) (BXC0205-BXC0215-BXC0187-BXC0173-BXC0222/ Biorexfars-Iran) (calorimetric method), as well as MDA (E0156Ra/ Crystal Day-China) and TAC (E0871Ra/ Crystal Day-China) (Eliza method), were measured using commercial colorimetric assay kits. Serum BUN and creatinine were quantified from terminal blood samples using corresponding colorimetric assay kits.

Urine was collected from each rat in individual metabolic cages over 24 hours on Day 28, following a 12-hour acclimation. Samples were maintained on ice, centrifuged at 3000 rpm for 10 minutes, aliquoted, and stored at −20 °C. Urinary albumin and urinary creatinine were measured using commercial colorimetric kits.

2.4. Histological Evaluation

The liver tissue of the animals was collected and then fixed in 10% neutral buffered formalin. Fixed tissues were sectioned at 5 μm thickness, and the sections were stained with hematoxylin and eosin (H&E). Microscopic (Nikon E200-Japan) examination was performed to assess histological alterations such as hepatocyte damage, inflammatory infiltration, and tissue architecture.

2.5. Statistical Analysis

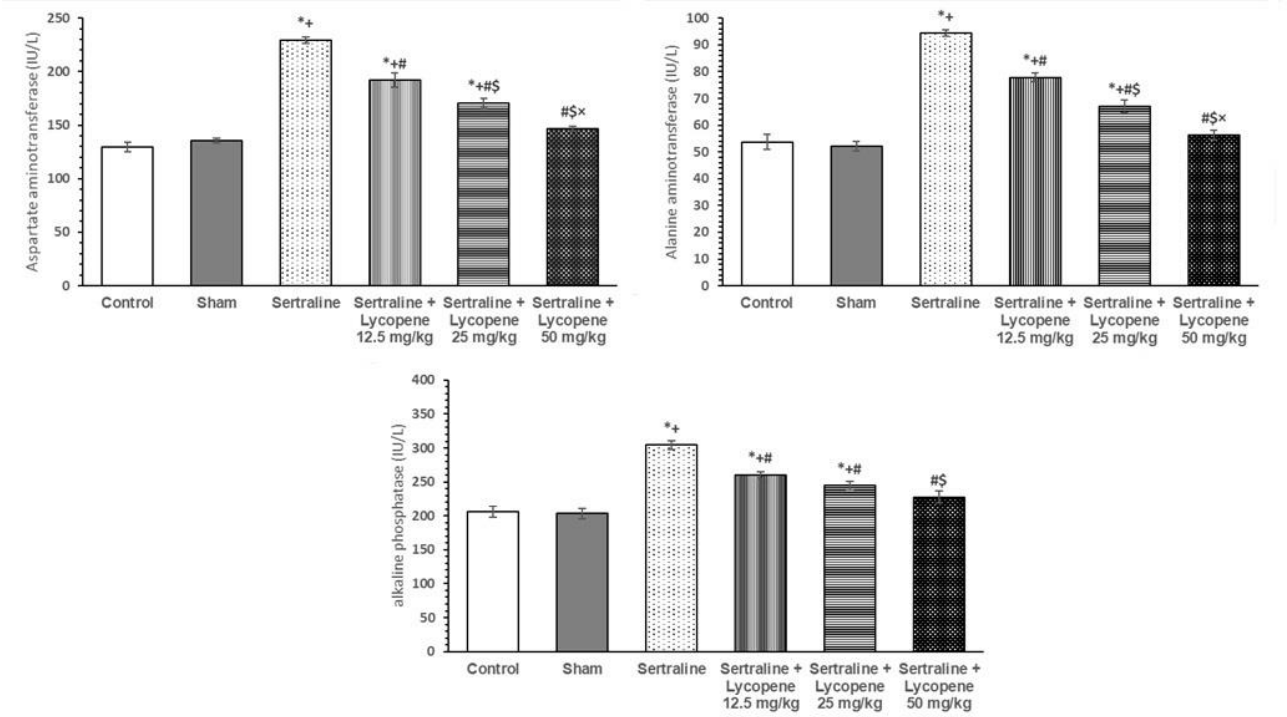
Data were analyzed using SPSS software version 21. The ordinariness of the information was surveyed utilizing the Kolmogorov-Smirnov test. Comparisons were done using one-way analysis of variance followed by Tukey's post hoc test. Results are reported as mean ± standard deviation, and $p \leq 0.05$ considered statistically significant.

3. Results

Body weight data showed consistent patterns across groups. In the control group, animals gained an average of 32.5 ± 3.02 grams of weight over 28 days. Sertraline-treated rats showed significant weight gain (19.33 ± 3.61 g), indicating potential systemic effects or appetite suppression. Lycopene supplementation reduced this decrease in a dose-dependent manner, with the 50 mg/kg group achieving a weight gain of 30.00 ± 1.26 g, which is very close to control values. These findings suggest a stabilizing influence of lycopene on body weight under pharmacological stress.

3.1.Liver Enzymes

Sertraline administration caused significant increase in ALT, AST, and ALP compared to the control and sham groups ($p<0.001$), indicating liver cell damage and cholestatic stress. Co-administration treatment with lycopene significantly reduced these increases in a dose-dependent manner. Using 50 mg/kg lycopene showed enzyme levels comparable to baseline, which was significantly decreased compared to the sertraline group ($p<0.001$). These findings suggest that lycopene modulates enzyme leakage associated with drug-induced liver stress (Graph 1).



Graph 1: Comparison of mean serum concentration of liver enzymes among different groups

* Compared to control

\+ Compared to sham

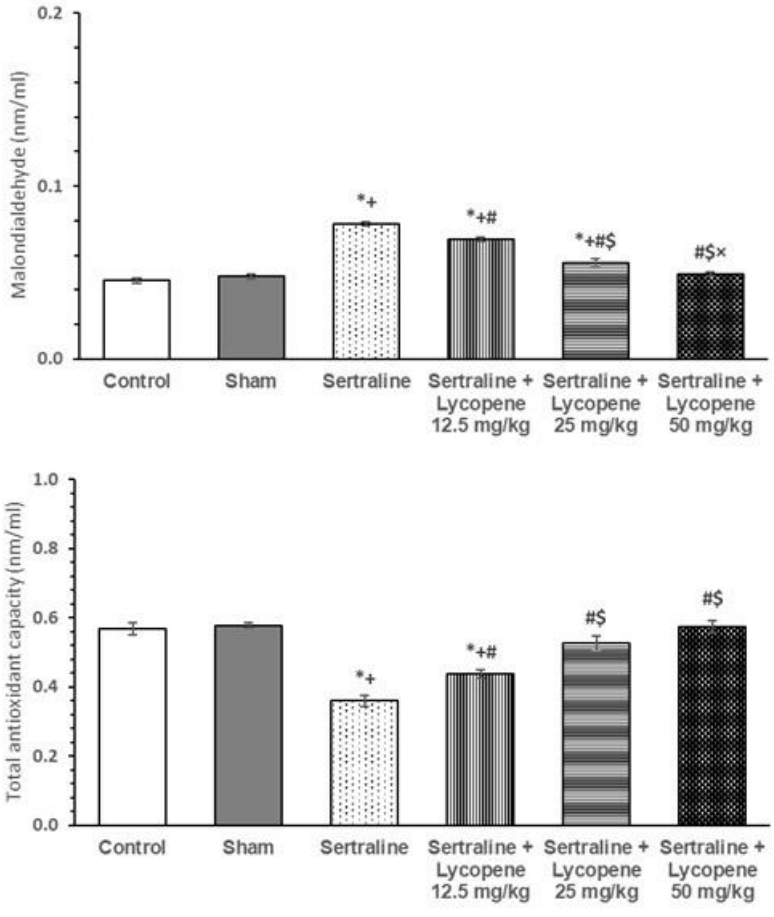
\# Compared to sertraline 0.5 mg/kg

$ Compared to sertraline 0.5 mg/kg + lycopene 12.5 mg/kg

× Compared to sertraline 0.5 mg/kg + lycopene 25 mg/k

3.2. Oxidative Stress and Antioxidant Status

Sertraline significantly increased serum MDA levels and decreased TAC compared to the untreated control group ($p<0.001$), confirming increased OS and decreased redox defense. Lycopene supplementation reversed these changes, with the highest dose restoring TAC and suppressing MDA concentrations to near-normal levels ($p<0.001$ vs. sertraline). The antioxidant effect of lycopene showed dose-dependent efficacy (Graph 2).



Graph 2: Comparison of mean serum oxidative stress and antioxidant status among different groups

* Compared to control

+ Compared to sham

Compared to sertraline 0.5 mg/kg

$ Compared to sertraline 0.5 mg/kg + lycopene 12.5 mg/kg

× Compared to sertraline 0.5 mg/kg + lycopene 25 mg/kg

3.3. Liver and Renal Function Markers

Liver and renal biomarkers are summarized in Table 1.Sertraline administration significantly increased serum total bilirubin compared to control ($p<0.001$), showing impaired hepatic clearance. Fifty mg/kg Lycopene reversed this effect and restored bilirubin levels to baseline ($p<0.001$ vs. sertraline). No significant variation in total protein and serum albumin were observed in the experimental groups ($p\leq0.05$), indicating maintenance of hepatic protein synthesis throughout the 28-day exposure period.

Urinary albumin concentration was also increased in the sertraline group ($p<0.001$ vs. control), indicating increased glomerular permeability or early renal involvement. Reduction in urinary albumin, with the 50 mg/kg group showing significant improvement compared to lower-dose sertraline and lycopene groups ($p<0.001$). Serum urea and creatinine levels remained within normal physiological ranges ($p\leq0.05$), indicating maintenance of renal filtration function throughout the study.

Sertraline administration did not significantly alter serum urea (BUN) or creatinine (Cr) levels compared to the control groups ($p\leq0.05$), indicating maintenance of renal filtration function throughout the study period. In all treatment groups, BUN and Cr values remained within the physiological range. These results suggest that although sertraline caused hepatic and oxidative disorders, its effects on glomerular filtration and renal excretory function were minimal during the 28-day exposure period. Lycopene supplementation did not impair renal function and may support its systemic safety profile when administered alongside hepatotoxic agents.

Table 1. Liver and Renal Function Markers

Parameter	Control	Sham	Sertraline	Lycopene 12.5 mg/kg	Lycopene 25 mg/kg	Lycopene 50 mg/kg
Total Bilirubin (mg/dL)	0.076 ± 0.017	0.079±0.01	0.215 ± 0.01 *+	0.138 ± 0.01 *+	0.102 ± 0.0067 *+ $	0.0787 ± 0.01 ×
Total Protein (g/dL)	7.517± 0.83	7.233±0.74	6.867 ± 0.45 (*ns*)	7.133 ± 0.42 (*ns*)	6.583± 0.20 (*ns*)	6.750 ± 0.48 (*ns*)
Albumin (g/dL)	3.116 ± 0.43	2.933±0.32	2.716 ± 0.41 (*ns*)	2.883 ± 0.28 (*ns*)	2.766 ± 0.20 (*ns*)	2.667 ± 0.15 (*ns*)

Urinary Albumin (UA) (mg/dL)	26.000 ± 1.63	24.985±1.55	30.003 ± 2.93 *+	27.830 ± 1.79 *+	25.331 ± 1.63 $	24.003 ± 1.41 $×
Urea (BUN) (mg/dL)	26.004± 1.00	27.504±2.88	27.667 ± 1.37 (*ns*)	25.667 ± 1.63 (*ns*)	26.673 ± 1.75 (*ns*)	26.171 ± 1.72 (*ns*)
Creatinine (Cr) (mg/dL)	0.581 ± 0.03	0.563±0.05	0.623 ± 0.06 (*ns*)	0.587 ± 0.06 (*ns*)	0.558 ± 0.05 (*ns*)	0.573 ± 0.04 (*ns*)

194 * Compared to control

195 + Compared to sham

196 # Compared to sertraline 0.5 mg/kg

197 $ Compared to sertraline 0.5 mg/kg + lycopene 12.5 mg/kg

198 × Compared to sertraline 0.5 mg/kg + lycopene 25 mg/kg

199

200 **3.4. Histopathological Results**

201 The histological evaluation of liver tissue is presented in Fig. 1. No pathological changes were shown
202 in the control and sham groups, indicating normal liver structure. In contrast, the sertraline-treated
203 group showed significant hepatic congestion, extensive infiltration of inflammatory cells, and
204 evidence of hemorrhage. Co-administration treatment with lycopene at a dose of 12.5 mg/kg did not
205 significantly reduce tissue damage; Intense infiltration of inflammatory cells and hemorrhage were
206 still prominent. At a dose of 25 mg/kg, lycopene moderately reduced the severity of lesions and
207 reduced the spread of inflammation and bleeding. Notably, the lycopene group at 50 mg/kg showed
208 only mild infiltration of inflammatory cells and minimal hemorrhage, with approximate preservation
209 of tissue structure, supporting a dose-dependent protective effect against sertraline-induced liver
210 injury (Fig. 1).

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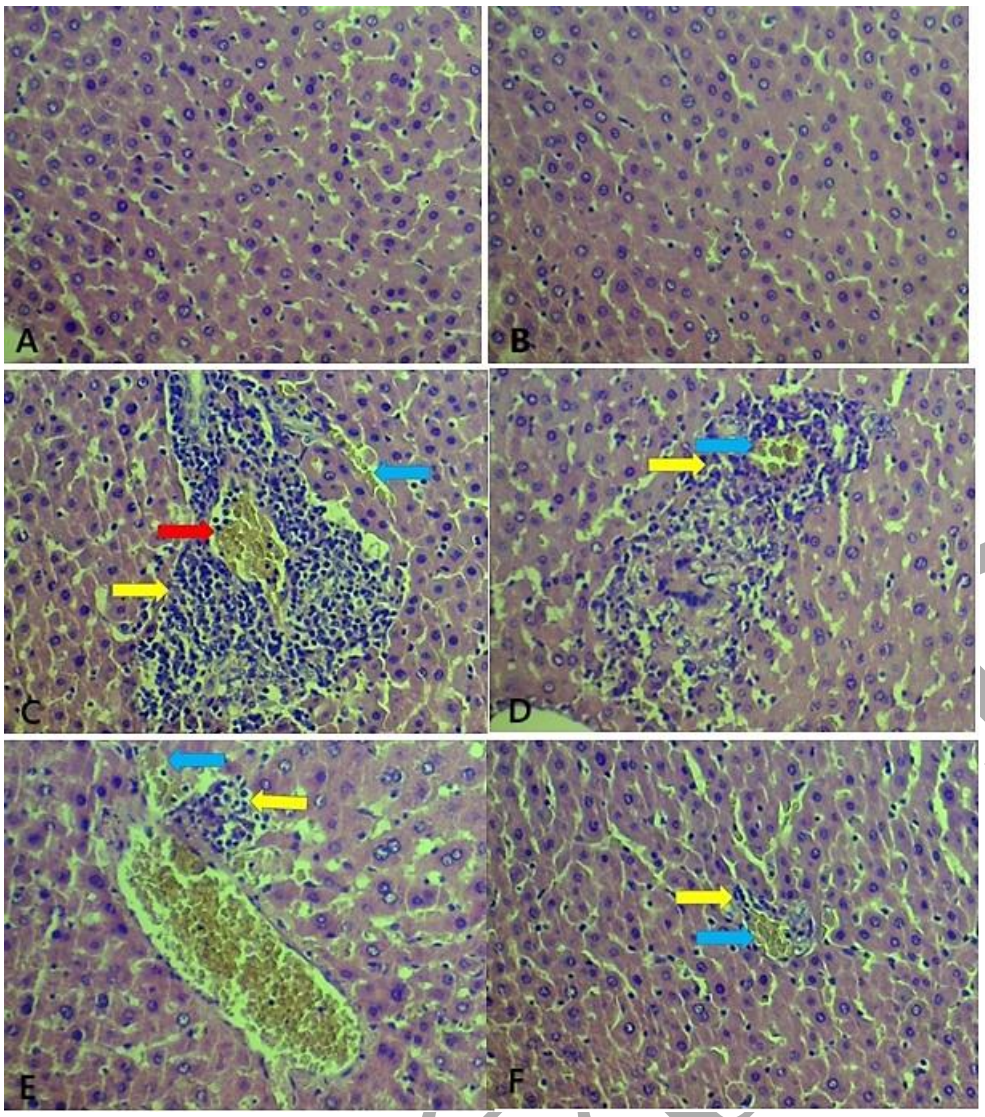

Fig. 1. Representative H&E-stained liver sections (magnification ×10) from experimental groups. (A) Control group: Normal hepatic architecture. (B) Sham group: Histologically unremarkable tissue, consistent with control. (C) Sertraline group: Severe congestion (red arrows), widespread infiltration of inflammatory cells (yellow arrows), and prominent hemorrhage (blue arrows). (D) Sertraline + Lycopene 12.5 mg/kg group: Extensive inflammatory cell infiltration (yellow arrows) and hemorrhage (blue arrows), similar to sertraline-only group. (E) Sertraline + Lycopene 25 mg/kg group: Moderate inflammatory changes and reduced hemorrhage. (F) Sertraline + Lycopene 50 mg/kg group: Mild inflammatory cell presence (yellow arrows) and minimal hemorrhage (blue arrows), with partial preservation of hepatic lobular structure.

4. Discussion

The current findings reveal that lycopene exerts a notable protective effect against sertraline-induced liver injury, as evidenced by decreased levels of ALP, ALT, AST, and total bilirubin. This biochemical improvement aligns with prior studies that underscore lycopene's antioxidant potential in mitigating chemically triggered hepatic damage. For instance, Dong et al. (2019) demonstrated that lycopene attenuates liver inflammation and suppresses LPS-induced enzyme elevation by

modulating NF-κB/COX-2 signaling, thereby maintaining hepatic architecture (13). Likewise, Abdul Naeem et al. (2023) reported that lycopene activates the Nrf2/HO-1 pathway, which contributes to reduced OS and limits enzyme leakage in chlorpyrifos-exposed models (14).

Contrary to the present findings, Mirahmadi et al. (2023) reported no statistically significant alterations in hepatic enzyme levels following lycopene administration in individuals with metabolic syndrome (9). They proposed that lycopene's efficacy may be contingent upon the specific pathophysiological context, with metabolic disorders potentially less amenable to antioxidant-based interventions than drug-induced liver injury. In contrast, the 50 mg/kg dose used in this study yielded pronounced hepatoprotective effects, corroborating the observations of Moore et al. (2023), who documented similar enzymatic stabilization in a model of silver nanoparticle-induced hepatic stress (15). The sustained normalization of liver enzymes across these toxicological models reinforces lycopene's potential as a pharmacological adjunct for mitigating hepatic damage in drug-exposed populations.

Lycopene hepatoprotective effects was in agreement with prior investigations into antioxidant-rich phytochemicals. For example, Winiarska-Mieczan et al. (2023) demonstrated that polyphenols mitigate enzyme elevation by suppressing reactive oxygen species (ROS) in neuroinflammatory models (16). Widely studied for its multifaceted bioactivity, lycopene has demonstrated hepatoprotective effects by dampening OS and inflammatory cascades, as evidenced in multiple preclinical models (15).

Lipid metabolism plays a fundamental role in energy homeostasis and regulation of inflammatory responses, and both are intricately linked to liver health (17). Lipogenesis, if dysregulated, may lead to aberrant fat accumulation and contribute to metabolic dysfunction. Elevated free fatty acids from persistent lipogenic activity may infiltrate non-adipose tissues such as the heart, liver, and pancreas, triggering cellular stress and lipotoxicity. Two key enzymes that drive this pathway include acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS). They catalyze the conversion of acetyl-CoA to malonyl-CoA and the subsequent formation of palmitate, respectively (18). Aberrant regulation of ACC and FAS has been implicated in the development of obesity and nonalcoholic fatty liver disease (NAFLD), in which chronic lipogenesis exacerbates hepatic lipid burden and OS (17, 19).

In contrast to lipogenesis, lipolysis servesas a protective catabolic mechanism that mobilizes stored triglycerides to fulfill systemic energy needs. This process is coordinated by a cascade of lipolytic enzymes, starting with adipose triglyceride lipase. Hormone-sensitive lipase and monoacylglycerol lipase then proceed, collectively releasing free fatty acids and glycerol for environmental use.

Increased regulated lipolysis enhances metabolic adaptation and may reduce hepatic lipid overload by balancing excessive lipid deposition (20). Emerging evidence suggests that bioactive compounds, including lycopene, can influence the dynamic equilibrium between lipogenesis and lipolysis (21). Wang et al. (2019) demonstrated that lycopene upregulates thermogenic and lipolytic gene expression, thereby suppressing lipogenic markers and conferring metabolic resilience in obese mice subjected to a Western diet (22). These findings expand the therapeutic scope of lycopene and suggest that its antioxidant properties may extend beyond liver cell protection to include regulatory roles in lipid metabolism—further supporting its utility in models of drug-induced liver injury.

This study show that lycopene exerts a protective effect against sertraline-induced OS in liver tissue. It is demonstrated by a significant decrease in serum MDA concentration and an increase in TAC. These comes about are steady with past discoveries by Abdul Naeem et al. (2023). They reported that Lycopene reduces chlorpyrifos-induced liver damage by activating the Nrf2/HO-1 signaling pathway, thereby restoring redox balance and improving histopathological outcomes.(14). Similarly, More et al. (2023) found that lycopene reduced MDA levels and increased antioxidant defense in models exposed to silver nanoparticles. This effect indicates a broad protective role against stress caused by xenobiotic factors (15).

Additional biochemical evidence from this study supports the mechanistic role of lycopene in regulating reactive oxygen species (ROS) and maintaining redox balance. The concurrent reduction in MDA and elevation in TAC implies that lycopene may increase key antioxidant enzymes such as SOD and GSH. This enzymatic modulation has been previously observed by Dong et al. (2019), who reported that lycopene attenuated liver injury in LPS-induced models through suppression of oxidative pathways. The reproducibility of these results across different hepatic stimuli highlights the role of lycopene not only as a radical scavenger but also as a modulator of intrinsic antioxidant defense systems (13).

Notably, investigations involving human cohorts have produced more variable outcomes. Interestingly, studies involving human populations have yielded more heterogeneous results. For instance, Mirahmadi et al. (2023) reported that lycopene did not produce significant changes in OS markers in patients with metabolic syndrome (9). Such discrepancy suggests differences in uptake, baseline redox status, or multifaceted nature of systemic inflammation in human injuries compared to the controlled conditions of animal models. Nevertheless, the present findings reaffirm that in the context of drug-induced liver injury—such as sertraline exposure—lycopene exhibits a significant antioxidant response. Taken together, the data suggest that lycopene supplementation may have therapeutic value in preserving liver function by reducing lipid peroxidation and increasing

antioxidant capacity, especially at higher doses. This highlights the importance of future research into dose responsiveness, bioavailability, and potential synergistic interactions with complementary compounds.

As previously noted, body weight trajectories showed a gradual change during the intervention period, which is consistent with observations reported by Chang et al. (2017). The author and colleagues noted that weight fluctuations often appear gradually during pharmacological or nutritional interventions (23). In our study, sertraline administration led to a marked suppression of weight gain, likely indicative of systemic stress responses and reduced appetite. Interestingly, lycopene supplementation counteracted this trend in a dose-dependent manner, with the 50 mg/kg group exhibiting near-normal weight gain compared to the control group.

This pattern may be attributed not only by antioxidant and anti-inflammatory effects, but also to its influence on lipid metabolic pathways. Previous research has shown that lycopene modulates critical signaling networks such as JNK/MAPK, AGE/RAGE, SIRT1/FoxO1/PPARγ, and PI3K/Akt, thereby enhancing metabolic efficiency and promoting fat loss (24). At the transcriptional level, lycopene upregulates the expression of lipolytic genes while concurrently downregulating lipogenic enzymes, including ACC and FAS. These enzymes are essential for the synthesis of endogenous fatty acids. Lipolytic activity is mediated by enzymes including adipose triglyceride lipase, monoacylglycerol lipase, and hormone-sensitive lipase. These enzymes mobilize energy reserves during metabolic stress (25). Lycopene's role in promoting this catabolic shift may explain the body weight stabilization observed in treated animals, suggesting a protective mechanism against sertraline-induced metabolic disruption (24). Taken together, these comes about propose that the effects of lycopene go beyond liver protection and encompass broader metabolic regulatory functions. This dual function provides a compelling therapeutic rationale for its use in pharmacological models that induce both hepatic and metabolic stress.

Conclusion

This study shows that lycopene administration significantly reduces sertraline-induced liver damage. This occurs with a decrease in the levels of key biochemical markers including AST, ALT, ALP, total bilirubin, and MDA, along with an increase in TAC. The hepatoprotective effects were more evident at higher doses, indicating a clear dose-dependent response. These results support the potential of lycopene as a therapeutic adjunct in the management of drug-induced hepatotoxicity. Further research is necessary to elucidate the precise molecular mechanisms, assess long-term efficacy, and confirm safety in clinical settings. These findings provide valuable insights for the development of

antioxidant-based herbal therapies, reinforce the role of natural compounds in liver protection, and may serve as guidance for clinicians considering integrated treatment strategies.

Acknowledgments

We sincerely thank all the laboratory animal center of Jahrom University of Medical Sciences, Jahrom, Iran.

Authors` contribution

E.B.J and H.K.J study concept and design. E.B.J, H.K.J, and A.S did experimental work, follow-ups, and analysis of statistical data. All authors drafting and reviewed the manuscript.

Ethics

The Research Ethical Committee of Jahrom University of Medical Sciences approved this study (Code of Ethics IR.JUMS.AEC.1403.009).

Conflict of Interest

No declare.

Data Availability

All information created or analyzed amid this venture are included within the article.

Funding

No Finding.

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