AMELIORATIVE EFFECT OF CURCUMIN ON MONOSODIUM GLUTAMATE INDUCED HEPATIC NECROSIS AND STEATOSIS IN WISTAR ALBINO RATS

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ABSTRACT

Objective: This study aimed to investigate the protective effects of curcumin against low dose monosodium glutamate (MSG) in chronic use-induced liver damage in rats, focusing on biochemical markers, lipid profiles, and histopathological changes.

Methods: Six groups of 36 adult male wistar albino rats were grouped as : control, MSG-treated, MSG+curcumin, MSG+silymarine, curcumin-treated, and silymarin-treated. Serum and liver enzyme levels, including hepatotoxicity indicators like AST, ALT, ALP, LDH, and GGT, were used to evaluate the liver function. Hepatic Steatosis indicators are TG, TL,TC, FFA, PL were measured in order to assess the lipid profile. In order to evaluate the structural damage, liver histology was analyzed.

Results: Low dose MSG in chronic exposure treatment significantly elevated the liver enzyme levels (AST, ALT, ALP, LDH, and GGT), increased lipid profiles (free fatty acids, phospholipids, total lipids, triglycerides, and total cholesterol), and also caused the severe histopathological damage. In contrast, curcumin treatment notably reduced these enzyme levels and improved lipid profiles, showing a protective effect on liver health. Histopathological analysis were demonstrated the significant preservation of liver architecture in the curcumin-treated group, comparable to the effects observed in the MSG treated group.

Conclusion: According to the findings, a low dose of MSG on chronic exposure markedly increased all hepatotoxic and hepatic steatosis indicators, and further histopathological consideration shows liver damage. Curcumin is equivalent to the common medication Silymarin and shown a significant ameliorative effect against MSG-induced hepatic necrosis and steatosis. Curcumin's anti-inflammatory, lipid-regulating, and antioxidant qualities enable it to demonstrate its hepatoprotective benefits.

Key Words: Monosodium Glutamate (MSG), Hepatic Necrosis, Hepatic Steatosis, Curcumin, Silymarin, Hepatoprotective and Anti-Lipidemic Effects.

Introduction:

The liver is consider as an essential organ for preserving metabolic equilibrium and also the crucial for energy storage, lipid metabolism, and detoxification. However, hepatotoxicity and chronic liver disorders can result from a variety of environmental and dietary poisons that weaken its resistance. Monosodium glutamate (MSG), a common flavoring agent in processed foods, is one of these toxins that has drawn attention due to its detrimental effects on liver function. Through processes including oxidative stress, lipid peroxidation, and dysregulated lipid metabolism, chronic exposure to MSG has been associated with hepatic steatosis, necrosis, and ultimately the development of severe liver damage. Even though MSG is widely used in the food industries, little is known about therapeutic approaches to prevent its hepatotoxic effects, which calls for more study. [1,2] Because of its well-established hepatotoxic potential in animal models and its applicability as a real-world food toxin, MSG was chosen as the inducing agent in this investigation. Additionally, MSG-induced hepatotoxicity provides a valid experimental model for examining the etiology of liver diseases such steatosis and necrosis, providing information on potential treatment approaches for liver damage brought on by toxins. [3,4,5] Natural substances have become appealing substitutes for traditional medications due to their safety records and pharmacological adaptability, making them interesting options for hepatoprotection. Among them, curcumin, the bioactive ingredient in turmeric (Curcuma longa), has drawn notice for its strong lipid-modulating, anti-inflammatory, and antioxidant properties. By scavenging reactive oxygen species (ROS), preventing lipid peroxidation, regulating inflammatory pathways, and reestablishing lipid homeostasis, curcumin may help prevent liver damage, according to studies[6,7]. It is a good option for treating liver damage brought on by toxins, such as MSG, because of its capacity to combat inflammation and oxidative stress. [8,9] Likewise, silymarin, a flavonolignan complex obtained from milk thistle, or Silybum marianum, is a well-known hepatoprotective substance with anti-inflammatory and antioxidant properties. In both experimental and clinical contexts, silymarin has shown effective in preserving liver function and lowering oxidative damage, making

it a commonly used reference chemical in liver research. Its application in this study acts as a standard by which to measure curcumin's effectiveness. [10, 11] This study examines the hepatoprotective and anti-lipidemic properties of curcumin using a wistar albino rat model of low dose MSG-induced liver necrosis and steatosis. By comparing their effectiveness, this study seeks to provide insight on the therapeutic potential of silymarin and curcumin for liver health. MSG is commonly added to meals as a flavor enhancer. Important evaluation criteria include lipid profiling, histological analysis of liver tissue, and common liver function markers such as alkaline phosphatase (ALP), alanine transaminase (ALT), and aspartate transaminase (AST). These methods enable a comprehensive assessment of liver function and structural integrity. [12] In this experimental research studies aims to address the lack of research on the effects of low-dose, chronic MSG exposure on liver health and curcumin hepatoprotective properties. Most studies have focused on high-dose MSG exposure, which may not accurately reflect real-world scenarios. This study aimed to investigate the hepatoprotective effects of curcumin against low-dose, chronic MSG exposure-induced liver damage and steatosis. We hypothesized that curcumin would counteract MSG toxicity, reducing liver damage and steatosis markers. By comparing the therapeutic efficacy of curcumin and standard treatment group silymarin and examining the low dosage of MSG-induced hepatotoxicity, this study opens the door to natural, affordable remedies for liver illnesses.

MATERIALS AND METHODS

Chemicals

Curcumin and silymarin were procured from Sigma-Aldrich Chemicals. Monosodium glutamate (MSG) and carboxymethylcellulose (CMC) were obtained from Viva Scientific Pvt. Ltd., Chennai. All other chemicals used in this study were of analytical grade and purchased locally.

Animals

Male Wistar albino rats weighing 120–150 grams were obtained from the primary animal house of the Sathyabama Research Center. The animals were housed in polypropylene cages with husk bedding under standard laboratory conditions, maintained at a temperature of 23 ± 4°C, relative humidity of 50–70%, and a 12-hour light/dark cycle. They were fed standard pellet meals and provided water ad libitum. The study was conducted following ethical guidelines after obtaining approval from the Institutional Animal Ethics Committee (IAEC Approval No. SU/CLATRI/IACE/VIII/061/2017).

Experimental Design

Thirty six male wistar albino rats were randomly divided into six groups with six animals in each. Group-I served as Control and received 0.7% carboxymethylcellulose (CMC) (0.3ml/100g b.w.), Group-II received MSG Alone, Group-III received MSG + Curcumin, Group-IV received MSG + Silymarin, Group-V received Curcumin Alone, and Group-VI received Silymarin Alone. MSG was administered at the dose of (4 mg/kg b.w.) [13] and Curcumin and Silymarin at (100mg/kg b.w.) [14,15] each. All the treatments were given orally for 60 days, MSG was given first followed by Curcumin and Silymarin. All the drug doses were selected based on the previous literature.

Blood Sample Collection

At the end of the experimental period, blood samples were collected from the retro-orbital plexus into plain centrifuge tubes. The samples were centrifuged at 2500 rpm for 30 minutes to separate the serum, which was then stored at 12–15°C in small vials for biochemical analysis.

Liver Tissue Preparation

Liver tissues (100 mg) were collected within three hours post-sacrifice, blotted dry, and homogenized in Tris-HCl buffer (0.01 M, pH 7.4) at 4°C. The homogenates were centrifuged at 2500 rpm for 30 minutes, and the supernatants were stored at 12–15°C for biochemical analysis within 48 hours.

Biochemical Measurements

Determination of marker enzymes of hepatotoxicity in serum and liver tissue of rats

The activities of marker enzymes of hepatotoxicity, Aspartate Transaminases (AST), Alanine Transaminases (ALT), were estimated according to Reitman and Frankel, 1957. [16] Alkaline Phosphatases (ALP) activity in serum and liver tissue were determined based on the method of King (1965a). [17] The serum and liver tissue Lactate dehydrogenases (LDH) and Gamma glutamyltransferases (GGT) activities were evaluated based on the methods of King (1965b) and Rosalki and Rao (1972). [18, 19]

Determination of hepatic steatosis markers in serum and liver tissue of rats

The levels of hepatic steatosis markers Total lipids (TL) and Triglycerides (TG) were determined according to the methods of Frings and Dunn (1970) and Rice (1970) respectively. [20, 21] Total Cholesterol (TC), Free Fatty acids (FFA) and Phospholipids (PL) were estimated in serum and liver tissue of rats according to the methods of Parekh and Jung (1970), Hron and Menahan (1981) and Rouser *et al.* (1970) respectively. [22, 23, 24]

Histopathological Examination

A portion of the liver was fixed in 10% neutral buffered formalin. Paraffin wax blocks were prepared, sectioned, and stained with hematoxylin and eosin (H&E) following the method of Bancroft and Cook. The sections were examined under a light microscope for histopathological changes [25].

Statistical Analysis

Data were expressed as mean ± SD. Statistical significance was evaluated using one-way analysis of variance (ANOVA) followed by Duncan's multiple range test for post-hoc comparisons. A p-value of <0.05 was considered statistically significant. Statistical analyses were conducted using GraphPad Prism software (version 7).

RESULTS

Effect of Curcumin on Marker Enzymes of Hepatotoxicity in Serum of MSG treated rats

Table-1

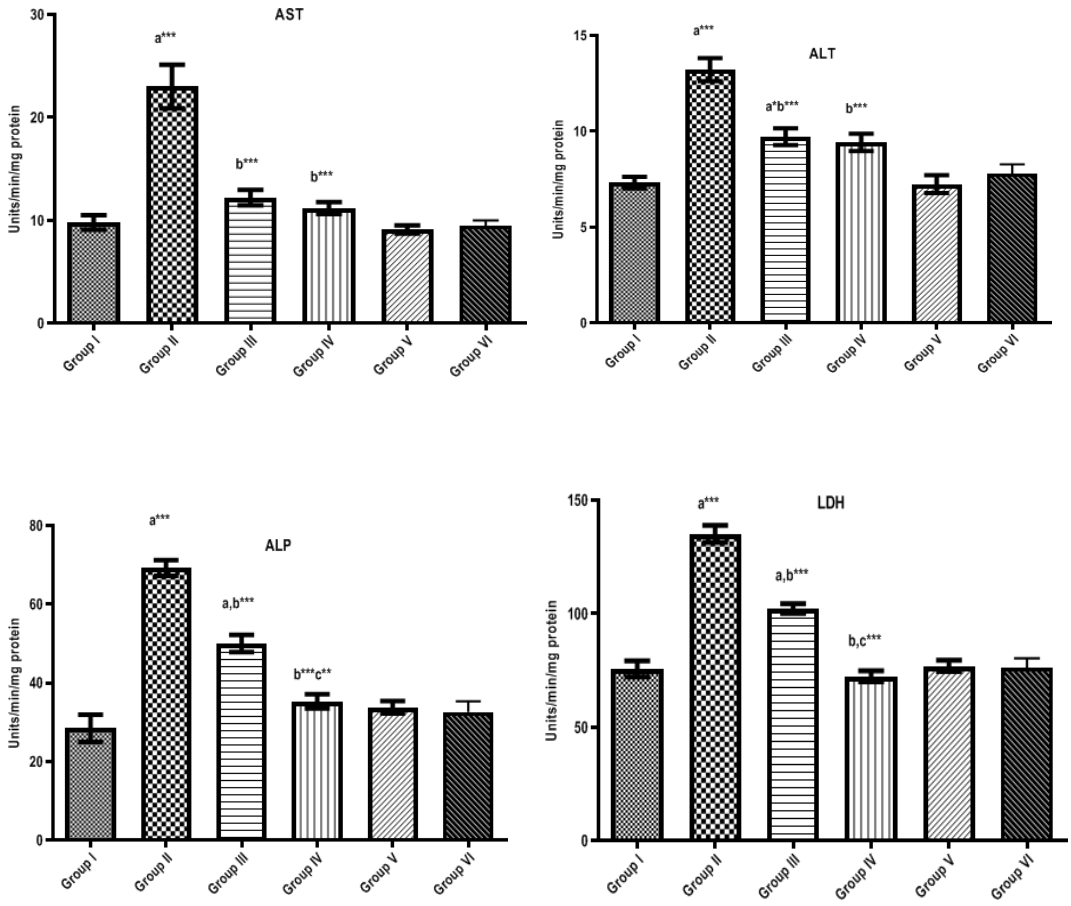
Groups	AST (U/L)	ALT (U/L)	ALP (U/L)	LDH (U/L)	GGT (U/L)
Group I	36.08 ± 1.9	29.14 ± 1.60	80.37 ± 2.9	251 ± 6.7	44.9 ± 2.09
Group II	71.8 ± 3.4 a***	66.05 ± 4.5 a***	196.7 ± 6.8 a***	379.4 ± 12.5 a***	92.7 ± 4.26 a***
Group III	52.3 ±1.2 a,b***	50.9 ± 2.27 a***b**	106 ± 3.97 a**, b***	293.4 ± 7.01 a**b***	72.6 ± 5.16 a***b**
Group IV	43.7 ± 1.6 b***	41.7 ± 1.4 a*b***	81.8 ± 2.25 b***c**	234.6 ± 6.64 b,c***	53.2 ± 3.13 b***c**
Group V	37.7 ± 2.2	33.5 ± 2.3	78.6 ± 4.92	222.9 ± 9 .4	41.9 ± 2.44
Group VI	38.98 ± 2.04	31.8 ± 2.6	83.38 ± 4.5	233 ± 7.14	44.1 ± 2.8

Table-1: The results are expressed as Mean ± S.D, (n = 6). MSG treatment significantly increased activities of all the marker enzymes of hepatotoxicity, while Curcumin significantly reversed it towards normalcy and was comparable to standard drug Silymarin. a. Denotes Group-I compared to Group-II, III, IV, V and VI. b. Denotes Group-II compared to Group-III and IV. c. Denotes Group-III compared to Group-IV. ** p<0.01; ***p<0.001.

The activities of marker enzymes of hepatotoxicity AST, ALT, ALP, LDH, and GGT in serum of rats treated for 60 days is presented in (Table-1). The impairement of liver function in MSG treated rats (Group-II) is evident from the highly significant (***p<0.001) two fold elevation in the levels of all the marker enzymes of hepatotoxicity in serum. Curcumin treatment effectively reversed (***p<0.001) the increase in the levels of all the hepatotoxic marker enzymes in serum towards normalcy and were similar to that of control and the standard hepatoprotective drug Silymarin. Curcumin alone and Silymarin alone treatments did not produce any change in the levels of all the marker enzymes and were comparable to Group-I.

Effect of Curcumin on Marker Enzymes of Hepatotoxicity in Liver tissue of MSG treated rats

Figure-1



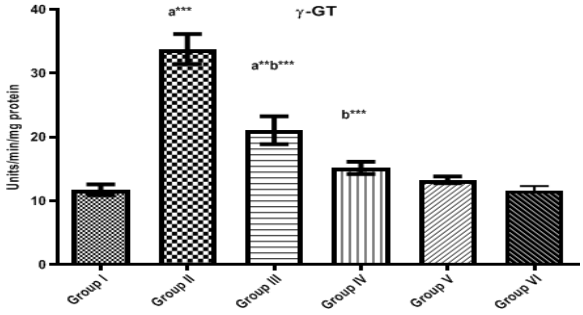


Figure-1 The results are expressed as Mean ± S.D, (n = 6). MSG treatment significantly increased activities of all the marker enzymes of hepatotoxicity, while Curcumin significantly reversed it towards normalcy and was comparable to standard drug Silymarin. a. Denotes Group-I compared to Group-II, III, IV, V and VI. b. Denotes Group-II compared to Group-III and IV. c. Denotes Group-III compared to Group-IV. ** $p<0.01$; ***$p<0.001$ The status of marker enzymes of hepatotoxicity AST,ALT, ALP, LDH, and GGT 60 days daily administration of MSG in liver tissue of rats are presented in (Figure-1). MSG induced (Group-II) hepatic damage was clearly evidenced by a highly significant (***$p<0.001$) two fold increase in the activities of all the marker enzymes of hepatotoxicity in liver tissue when compared to control (Group-I). MSG + CUR treatment (Group-III) highly significantly (***$p<0.001$) prevented this increase in the status of all hepatotoxic marker enzymes in liver tissue towards normalcy and were similar to that of control and the standard hepatoprotective drug SIL (Group-IV). CUR alone (Group-V) and SIL alone (Group-VI) treatments did not produce any change in the levels of all the marker enzymes and were similar to that of Group-I.

Effect of Curcumin on Hepatic Steatosis Markers in Serum of MSG treated rats

Table-2

Groups	TL	Tc	PL	FFA	TG
Group I	166.5 ± 6.30	76.78 ± 3.32	112.2 ± 5.7	83.73 ± 3.45	129.5 ± 4.05
Group II	297.6 ± 8.27 a***	199.9 ± 7.01 a***	249.5 ± 12.6 a***	193.5 ± 7.78 a***	250.6 ± 13.41 a***
Group III	205.1 ± 5.31 a,b***	119.3 ± 5.06 a,b***	129.2 ± 5.7 b***	118 ± 3.45 a,b***	156.1 ± 4.8 b***
Group IV	169.9 ± 4.64 b***c**	102.8 ± 4.8 a**,b***	102.6 ± 5.4 b***	97.25 ± 3.32 b***c*	128.9 ± 0.8 b***
Group V	162.5 ± 3.82	86.51 ± 3.6	90.17 ± 3.9	89.08 ± 3.98	123.8 ± 4.9
Group VI	165.6 ± 4.39	81.96 ± 3.7	88.98 ± 3.39	83.41 ± 1.87	128.5 ± 3.4

Table-2 :The results are expressed as Mean ± S.D, (n = 6). MSG treatment significantly increased levels of all the marker enzymes of hepatic steatosis, while Curcumin significantly reversed it towards normalcy and was comparable to standard drug Silymarin. a. Denotes Group-I compared to Group-II, III, IV, V and VI. b. Denotes Group-II compared to Group-III and IV. c. Denotes Group-III compared to Group-IV. *p<0.05; ** p<0.01; ***p<0.001. Table-2 shows the levels of hepatic steatosis markers, TL, TG, CHL, FFA and PL in serum of rats treated for 60 days. MSG induced hepatic steatosis is evident from the significant (***p<0.001) two fold elevation in the levels of all the markers of hepatic steatosis parameters in serum. Curcumin treatment effectively (***p<0.001) reversed the increase in the levels of all the hepatic steatosis parameters in serum towards normalcy and were similar

to that of control and the standard hepatoprotective drug SIL. CUR alone and SIL alone treatments did not produce any change in the levels of these marker enzymes and were comparable to Group-I.

Effect of Curcumin on hepatic steatosis markers in liver tissue of MSG treated rats

Figure-2

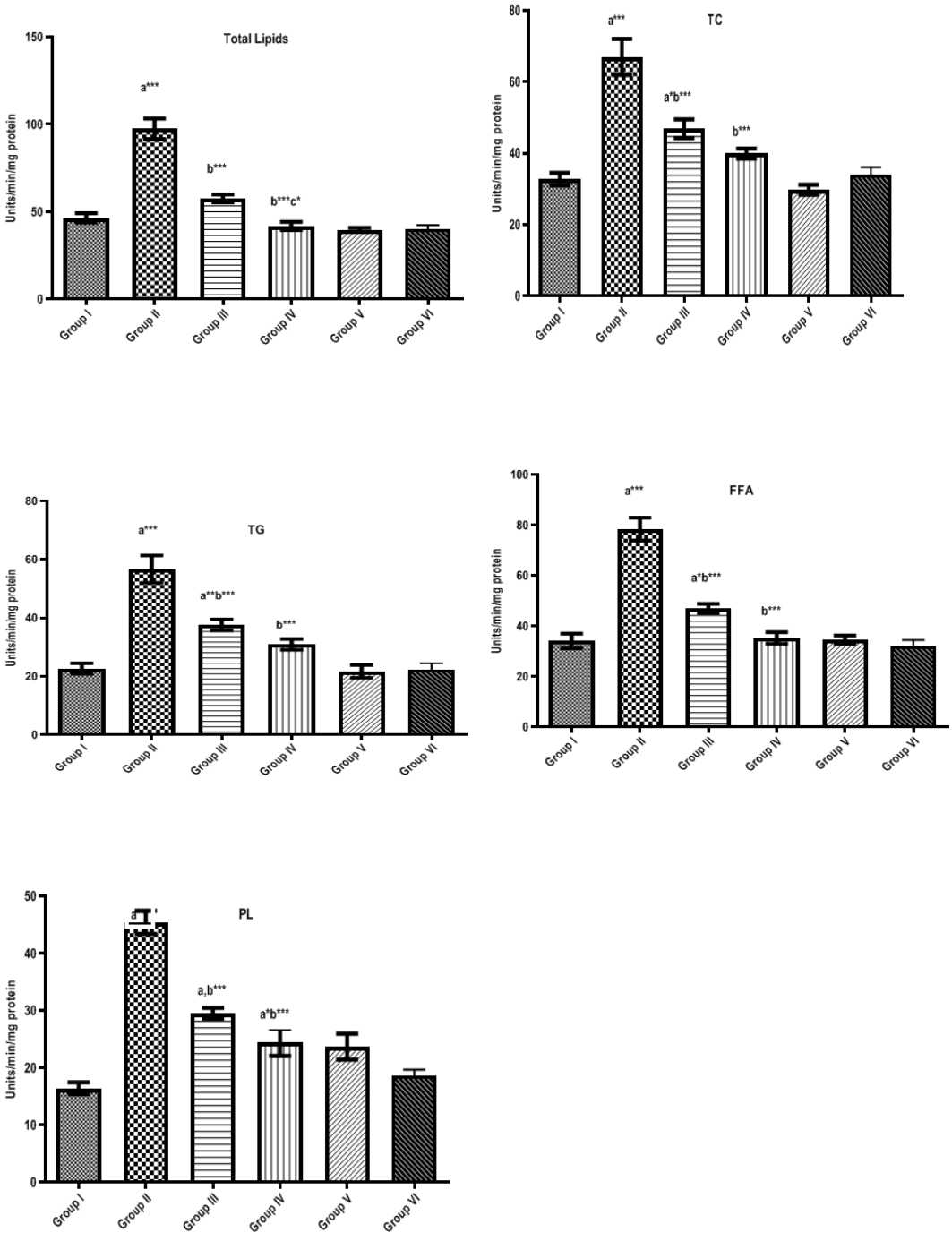
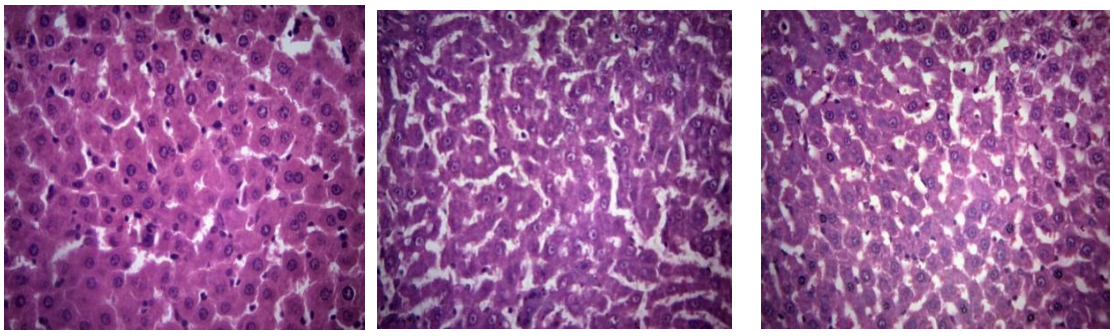


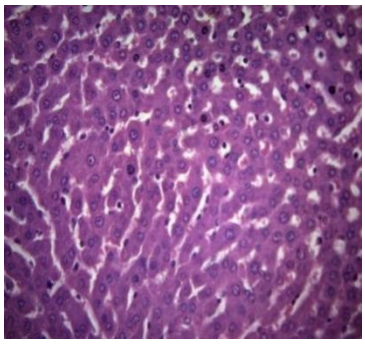
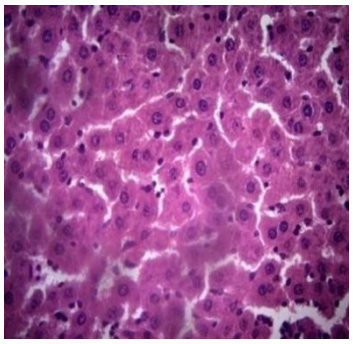
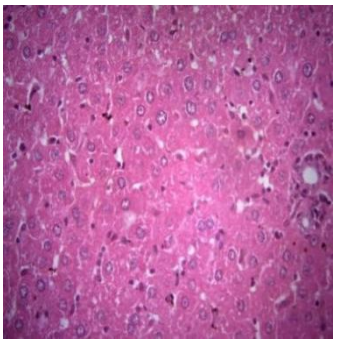
Figure-2:The results are expressed as Mean ± S.D, (n = 6). MSG treatment significantly increased levels of all the marker enzymes of hepatic steatosis, while Curcumin significantly reversed it towards normalcy and was comparable to standard drug Silymarin. a. Denotes Group-I compared to Group-II, III, IV, V and VI. b. Denotes Group-II compared to Group-III and IV. c. Denotes Group-III compared to Group-IV. *p<0.05; ** p<0.01; ***p<0.001 The levels of hepatic steatosis markers, TL, TG, CHL, FFA and PL in liver tissue of rats treated for 60 days is presented in (Figure-2). A highly significant (***p<0.001) two fold elevation in the levels of all the lipid parameters in liver tissue of rats indicates MSG alone (Group-II) induced hepatic steatosis. Treatment with CUR effectively reversed (***p<0.001) the increase in the levels of all the steatosis parameters in liver tissue towards normalcy and were similar to that of control and the standard hepatoprotective drug SIL. CUR alone and SIL alone treatments did not produce any change in the levels of these parameters and were comparable to control.

Effect of Curcumin on histopathological alterations in liver tissue of MSG treated rats

Figure-3



a. Group I–Control **b. Group II-MSG Alone** **c. Group III- MSG+CUR**

d. Group IV-MSG+SIL **e. Group V-CUR Alone** **f. Group VI-SIL Alone**

a. Group-I Control: Photomicrograph of normal hepatic tissues showing intact liver parenchyma with radiating hepatocytes containing normal nucleus depicts no signs of hepatic pathology. b. Group-II MSG alone: Photomicrograph of hepatic tissue treated with MSG showing abnormal hepatic archietecture. Nuclues is distorted and shrunken with condensed chromatin, increased eosonophilic cytoplasm, necrosis and small micro-vesicular lipid droplets indicating mild hepatic steatosis. Depicts signs of hepatic pathology. c. Group-III MSG + CUR: Photomicrograph of hepatic tissue treated with MSG and CUR showing hepatocytes of abnormal cytoplasmic architecture, micro-vesicular lipid droplets depicting very mild hepatic steatosis, also contains normal uniform hepatocytes with regular vesicular nuclei depicting curcumin's promising results with partial restoration of liver architecture. d. Group-IV MSG + SIL: Photomicrograph of hepatic tissue treated with MSG and SIL showing uniform hepatocytes, with reduced signs of necrosis and inflammation. Depicts the protective effect of SIL in MSG-induced liver damage. e. Group-V CUR Alone: Photomicrograph of hepatic tissue treated with CUR alone showing normal liver structure. f. Group-VI SIL Alone: Photomicrograph of hepatic tissue treated with SIL alone showing well-organized hepatocytes. The histopathological changes in the liver tissue of rats treated for 60 days is presented in (Figure-3). The histopathological examination of the liver tissue of control group showed normal

architecture, with well-preserved hepatocytes and clear sinusoidal structures. There were no signs of necrosis or inflammation. Liver of MSG alone treated rats (Group-II) showed significant damage to the liver architecture, including widespread necrosis, irregular hepatocyte shapes, cell infiltration, and disruption of sinusoidal spaces. The hepatic lobules were disorganized, indicating severe liver injury. Curcumin treatment (Group-III) showed promising results, with partial restoration of liver architecture. Hepatocytes appeared more organized, with reduced necrosis and minimal inflammatory cell infiltration compared to the MSG treated rats. The hepatic structure was more intact, suggesting curcumin's hepatoprotective effect. Silymarin treatment (Group-IV) led to significant improvement in liver structure. Hepatocytes were more uniform, with reduced signs of necrosis and inflammation. The treatment resulted in a clearer sinusoidal arrangement, indicating effective protection against MSG-induced liver damage. Curcumin alone (Grouip-V), as a treatment, also demonstrated effective restoration of liver structure. Hepatocyte arrangement was better, with reduced necrotic areas and fewer inflammatory cells, suggesting its protective role in maintaining liver integrity. Silymarin alone (Group-VI) showed a similar effect to curcumin in restoring liver architecture, with hepatocytes appearing well-organized and reduced necrosis. There was a notable reduction in inflammatory cell infiltration, supporting its hepatoprotective effects.

Discussion

The current study set out to evaluate curcumin's hepatoprotective and anti-lipidemic qualities against low dose monosodium glutamate (MSG) on chronic exposure -induced liver necrosis and steatosis in Wistar albino rats. Although MSG is frequently used as a taste enhancer, prolonged usage has been connected to inflammation, oxidative stress, and abnormalities in lipid metabolism, which can lead to hepatotoxicity, liver dysfunction, and histological changes [26,27]. These

conclusions are corroborated by our results, which demonstrate considerable liver damage in the MSG-treated group (Group II), as evidenced by increased biochemical markers, aberrant lipid profiles, and notable histological alterations. The progressive process of MSG-induced liver damage is facilitated by inflammation, oxidative stress, and metabolic abnormalities. It has been demonstrated that long-term, chronic exposure to MSG, such as 60 days, may reproduce the cumulative hepatotoxic effects seen in people who consume diets high in MSG over extended periods of time [28,29]. This is corroborated by research showing that liver necrosis, steatosis, and altered lipid metabolism occur after 6–12 weeks of exposure to MSG [26]. The two main signs of liver damage from toxins like MSG are hepatic necrosis and steatosis, where hepatocyte injury results in the release of intracellular enzymes like AST, ALT, and LDH into the bloodstream, as we found in our study [28]. The MSG-treated group showed severe necrotic changes, including elevated liver enzymes, inflammatory cell infiltration, and lobular disarray, which are in line with other studies that link MSG exposure to oxidative stress-induced hepatocyte damage [29]. Excessive lipid buildup in hepatocytes as a result of poor lipid metabolism causes hepatic steatosis, also known as fatty liver. Significant steatosis was caused by MSG consumption in this investigation, as seen by increased levels of triglycerides, cholesterol, and free fatty acids (FFA). Increased lipogenesis and decreased lipid catabolism are the causes of these alterations, which are made worse by oxidative stress and inflammatory cytokines [28]. Treatment with curcumin considerably reduced the effects of MSG-induced liver damage, supporting the idea that it has hepatoprotective properties. Curcumin's antioxidant and anti-inflammatory qualities increased hepatocyte integrity, restored lipid homeostasis, and decreased steatosis and necrosis. In line with previous studies of curcumin's capacity to mitigate oxidative stress and regulate inflammatory pathways, these effects were demonstrated by decreased levels of AST, ALT, ALP, LDH, and GGT in the curcumin-treated groups (Group III and Group VI) [30, 31]. The MSG-treated group had noticeably elevated levels of AST, ALT, ALP, LDH, and GGT, which may indicate liver injury and compromised cellular integrity. Hepatocyte necrosis and enhanced membrane

permeability are indicated by raised AST and ALT levels, whereas cholestasis and bile duct injury are suggested by elevated ALP and GGT readings. These results are in line with those of Chandra et al. (2020), who emphasized how MSG-induced oxidative stress drives these kinds of biochemical changes in the liver [32,33]. These results were corroborated by histopathological investigation, which showed notable enhancements in hepatic architecture in curcumin-treated groups, including decreased lipid droplet formation, inflammation, and necrosis. This is consistent with findings that curcumin enhances tissue repair, lowers inflammatory responses, and stabilizes hepatocyte membranes [34, 35]. Curcumin's lipid-regulating qualities are demonstrated by its capacity to normalize lipid profiles, which includes decreases in triglycerides, cholesterol, and FFAs. These effects might be explained by curcumin's capacity to lower lipid peroxidation and its impact on the expression of genes linked to lipid production and metabolism [28, 29]. Curcumin and silymarin, a well-known hepatoprotective drug, were equally effective in repairing histopathological architecture, lipid profiles, and liver enzyme levels [34, 35]. As indicated by lower ALP and GGT levels, both therapies enhanced bile flow and hepatobiliary function. The same results highlight curcumin's potential as a substitute hepatoprotective drug, especially in environments with low resources [26,27]. This study investigates curcumin as a natural, cost-effective substitute for synthetic hepatoprotective medications, filling a major research vacuum in hepatotoxicity. Although long-term liver damage caused by modest doses of MSG is well-established, there are few focused treatment approaches. Because of its many pharmacological advantages, such as its lipid-modulating, anti-inflammatory, and antioxidant properties, curcumin is a prospective treatment option for liver diseases brought on by dietary toxins. Even though this study offers compelling proof of curcumin's effectiveness, more investigation is necessary to pinpoint its exact molecular routes and processes. To confirm these results in human populations at risk of exposure to food toxins, clinical investigations are also required.

Conclusion

Curcumin's hepatoprotective and anti-lipidemic properties were demonstrated when it successfully reduced the liver necrosis and steatosis caused by chronic low doses of MSG. Curcumin's promise as a natural, affordable treatment for liver diseases linked to hepatotoxicity and lipid dysregulation . These results add to the increasing amount of data demonstrating curcumin's hepatoprotective properties and highlight its applicability in treating public health issues associated with long-term exposure to low dose dietary toxins msg.

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