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CURCUMIN MITIGATES MONOSODIUM GLUTAMATE INDUCED OXIDATIVE STRESS AND HEPATOTOXICITY VIA ALTERATION OF NRF2 GENE EXPRESSION IN WISTAR ALBINO RATS

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ABSTRACT

Monosodium glutamate (MSG) is the sodium salt of glutamic acid, commonly used as a flavor enhancer. Despite its taste stimulation and improved appetite enhancement, reports indicate that MSG is toxic to human and experimental animals. Low dose MSG on chronic exposure has been shown to induce oxidative stress, and hence finding an effective hepatoprotective agent is very essential. This study evaluates the hepatoprotective and antioxidant effects of Curcumin (CUR) against MSG induced oxidative stress in rats. Group-I rats received 0.7% carboxymethylcellulose (CMC) orally and served as control. Group-II rats administered with MSG (4mg/kg b.w p.o.). Group-III and IV received MSG followed by CUR and silymarin (SIL) both at (100mg/kg b.w p.o) respectively. Group-V and VI treated with CUR and SIL alone. All the treatments were administered for 60 days. Marker enzymes of hepatotoxicity AST, ALT and ALP were estimated in serum and liver tissue. Indicators of oxidative stress (LPO, SOD, CAT, GSH, GPX, GR, GST), membrane bound ATPase (Na2+ATPase, Mg2+ATPase and Ca2+ATPase) and histopathology were evaluated in liver tissue. Western blotting and Immunocytochemistry were used to determine the expression levels of nuclear factor erythroid 2 related factor (Nrf2). The results revealed that significant alterations in all the markers of hepatotoxicity, oxidative stress, membrane bound enzymes and Nrf2 gene expression caused by low dose MSG on

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chronic exposure were effectively mitigated by CUR treatment indicating its hepatoprotective and antioxidant properties.

KEYWORDS: Monosodium Glutamate; Curcumin; Hepatotoxicity; Oxidative Stress; Antioxidants; Nrf2.

LA CURCUMINA MITIGA EL ESTRÉS OXIDATIVO Y LA HEPATOTOXICIDAD INDUCIDOS POR EL GLUTAMATO MONOSÓDICO MEDIANTE LA ALTERACIÓN DE LA EXPRESIÓN DEL GEN NRF2 EN RATAS ALBINAS WISTAR

RESUMEN

El glutamato monosódico (GMS) es la sal sódica del ácido glutámico, comúnmente utilizado como potenciador del sabor. A pesar de su capacidad para estimular el gusto y aumentar el apetito, los informes indican que el GMS es tóxico para humanos y animales de experimentación. Se ha demostrado que la exposición crónica al GMS en dosis bajas induce estrés oxidativo, por lo que es fundamental encontrar un agente hepatoprotector eficaz. Este estudio evalúa los efectos hepatoprotectores y antioxidantes de la curcumina (CUR) contra el estrés oxidativo inducido por el GMS en ratas. Las ratas del grupo I recibieron carboximetilcelulosa (CMC) al 0,7 % por vía oral y sirvieron como control. Las ratas del

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grupo II recibieron GMS (4 mg/kg de peso corporal por vía oral). Los grupos III y IV recibieron GMS seguido de CUR y silimarina (SIL), ambas a 100 mg/kg de peso corporal por vía oral, respectivamente. Los grupos V y VI se trataron solo con CUR y SIL. Todos los tratamientos se administraron durante 60 días. Las enzimas marcadoras de hepatotoxicidad AST, ALT y ALP se estimaron en suero y tejido hepático. Los indicadores de estrés oxidativo (LPO, SOD, CAT, GSH, GPX, GR, GST), ATPasa unida a membrana (Na2+ATPasa, Mg2+ATPasa y Ca2+ATPasa) e histopatología se evaluaron en tejido hepático. Se utilizaron transferencia Western e inmunocitoquímica para determinar los niveles de expresión del factor nuclear eritroide 2 relacionado con el factor (Nrf2). Los resultados revelaron que las alteraciones significativas en todos los marcadores de hepatotoxicidad, estrés oxidativo, enzimas unidas a membrana y expresión del gen Nrf2 causadas por dosis bajas de MSG en exposición crónica se mitigaron eficazmente mediante el tratamiento con CUR, lo que indica sus propiedades hepatoprotectoras y antioxidantes.

PALABRAS CLAVE: Glutamato monosódico; curcumina; hepatotoxicidad; estrés oxidativo; antioxidantes; Nrf2.

INTRODUCTION

In modern food processing and preparation, monosodium glutamate (MSG), commonly known as "AJI-NOMOTO," serves as a widely utilized flavor enhancer. This sodium salt

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derivative of glutamic acid, comprising approximately 78% glutamic acid and 22% sodium with water, contributes a distinctive umami flavor to processed foods, restaurant dishes, and packaged products[1]. While regulatory agencies generally recognize MSG as safe, its increasing presence in processed food-rich diets has sparked growing concerns regarding chronic or excessive consumption[2,3]. Previous studies have associated MSG consumption with various adverse effects, collectively termed "Chinese restaurant syndrome," encompassing metabolic disorders, neurological toxicity, reproductive impairments, and hepatic dysfunction[3,4]. Recent studies demonstrate that MSG-induced hepatotoxicity manifests through multiple mechanisms, including lipid peroxidation, oxidative stress, and compromised antioxidant defense systems, potentially leading to liver necrosis, steatosis, fibrosis, and inflammation[5,6]. The liver's susceptibility to MSG-induced oxidative damage is particularly concerning given its crucial role in metabolism, detoxification, and maintaining physiological homeostasis[7]. The mechanism of MSG-induced liver injury primarily centers on oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) production and antioxidant defenses. This imbalance triggers mitochondrial dysfunction, lipid peroxidation, and cellular damage, accompanied by the depletion of essential antioxidant enzymes, including superoxide dismutase (SOD) and catalase (CAT)[8,9]. The central

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role of oxidative stress in the progression of various liver diseases, from fibrosis to hepatocellular carcinoma, underscores the importance of developing effective protective strategies.

Natural compounds with antioxidant properties have emerged as promising therapeutic agents against oxidative liver damage. Curcumin, a polyphenolic compound derived from Curcuma longa (turmeric), has demonstrated remarkable antioxidant and anti-inflammatory properties across various experimental models[10]. Its mechanism of action includes free radical scavenging, modulation of oxidative stress pathways, and enhancement of cellular antioxidant defense systems[11]. Curcumin's ability to support liver detoxification processes and mitigate inflammation, positions it as a potential therapeutic agent for managing oxidative stress-induced liver damage[12]. Silymarin, a standardized extract from milk thistle (Silybum marianum), has garnered significant attention in hepatoprotective therapy. This flavonoid complex exhibits potent antioxidant, anti-inflammatory, and membrane-stabilizing properties, making it a well-established reference compound in hepatoprotective studies[13]. Silymarin's mechanism of action involves free radical scavenging, enhancement of cellular glutathione levels, and modulation of inflammatory mediators, complementing its ability to stabilize cell membranes and promote hepatocyte regeneration[14]. Its proven efficacy in various liver disorders has established it

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as a standard hepatoprotective agent against which novel treatments are often compared.

Nuclear factor-erythroid 2-related factor (Nrf2) a transcription factor, when activated by oxidative stress, causes increased gene expression of many antioxidant enzymes (CAT, SOD, GST) and phase II detoxifying enzymes (HO1, NQO1). Nrf2 plays a pivotal role in antioxidation and maintaining oxidative stress balance by regulating these genes. In *in vivo* conditions Nrf2 is sequestered in cells by Kelch-like ECH-associated protein1 (keap1) which is then ubiquitinated and degraded. When reactive oxygen species (ROS) are increased the Keap1 and Nrf2 are decreased, Nrf2 binds to Antioxidant Response Elements (ARE), and aids in transcription of down stream genes. Eventhough many studies have shown the importance of Nrf2 in regulating oxidative stress in many organs, none have understood the underlying precise molecular mechanisms in liver. Many chemical compounds obtained from plants have been shown to activate Nrf2 gene expression[15,16]. CUR exhibits many of its beneficial effects by activation of Nrf2 pathway.

This study aims to systematically evaluate the hepatoprotective and antioxidant potential of CUR demonstrated significant hepatoprotective activity against low-dose MSG chronic exposure-induced liver damage. Notably, curcumin's hepatoprotective effects were

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comparable to those of silymarin, a standard drug known for its liver-protective properties. CUR effectively mitigated oxidative stress, restored membrane ATPase activity, and modulated Nrf2 gene expression, which were disrupted by chronic low dose MSG exposure. Histopathological studies further confirmed the hepatoprotective effect of CUR showing significant improvements in liver tissue architecture and cellular morphology. These findings suggest that curcumin, a natural polyphenol, may be a protecting against low dose MSG on chronic exposure-induced liver damage.

MATERIALS AND METHODS

Chemicals

Chemicals subatances like CUR and SIL were purchased from Sigma-Aldrich Chemicals. MSG and Carboxymethylcellulose (CMC) were obtained from Viva Scientific Pvt. Ltd., Chennai. All other chemicals used in this study were of analar grade and purchased locally.

Animals

For this study, male wistar albino rats weighing 120–150 grams were acquired from the Sathyabama Research Center's primary animal house. The animals were kept in polypropylene cages with husk bedding, with a 12-hour light/dark cycle, a temperature of 23 ± 4℃, and a relative humidity of 50–70% and were provided standard pellet feed and water ad libitum. The animal experiments were carried out

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after getting prior approval from the Institutional Animal Ethics Committee (IAEC Approval No.SU /CLATRI /IACE /VIII/ 061/2017).

Dosing Regimen

- MSG: Administered orally at 4 mg/kg body weight [17] daily for 60 days.
- Curcumin and Silymarin: Administered orally at 100 mg/kg body weight [18, 19] daily for 60 days.

Experimental Design

Male wistar albino rats were divided into six groups with 6 animals in each group. Group-I rats received a dose of 0.7% CMC at (0.3ml/100g b.w.p.o.) daily for 60 days and served as Control, Group-II rats were administered MSG Alone at a dose of (4 mg/kg b.w.p.o.) 60 days daily. Group-III rats received MSG + CUR, Group-IV rats received MSG + SIL, Group-V rats received CUR Alone, and Group-VI rats received SIL Alone. CUR and SIL were administered at the dose of (100mg/kg b.w.p.o.) each daily for 60 days. In Group-III, and Group-IV treats MSG was given first followed by CUR and SIL respectively.

Sample Collections and Tissue preparstion

At the end of the experiment period the blood samples were collected from rats retro orbital plexus into plain centrifuge tubes and kept at 45º C, centrifuged at 2500rpm for 30 min. Serum was separated and stored at 12-15 ºC in small vials for biochemical

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investigations. Animals were sacrificed at the end of the experiment. Liver were dissected out for further investigations. Liver tissue samples weighing 100 mg were collected within the three hours post-sacrifice, blotted dry, and homogenized in Tris-HCl buffer (0.01M, pH 7.4) at 4°C. The homogenate substances were centrifuged at the speed of 2500 rpm for the duration of 30 minutes . The supernatants were stored at 12–15℃ and analyzed within 48 hours.

Biochemical Measurements

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

The activities of marker enzymes of hepatotoxicity, Aspartate Transaminases (AST), Alanine Transaminases (ALT), were estimated in serum and liver tissue samples according to Reitman and Frankel[20]. Alkaline Phosphatases (ALP) activity in serum and liver tissue was determined based on the method of King[21].

Determination of oxidative stress markers in the Liver tissue of rats

Biochemical analyses were conducted using established methodologies. Lipid peroxidation (LPO) in liver homogenate was determined by the method of Ohkawa et al.,[22] , Reduced glutathione (GSH) levels in liver tissue were determined following Ellman with minor modifications by Beutler et al.,[23,24.] Activities of enzymatic antioxidants, including superoxide dismutase (SOD) and catalase (CAT), were assessed using the methods of Marklund and Marklund

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and Sinha, respectively[25,26].The activity of glutathione-S-transferase (GST) was evaluated using the method of Habig et al.,[27] , and glutathione peroxidase (GPx) activity was determined as per Rotruck et al.,[28] and Beutler et al.,[24]. Glutathione reductase (GR) activity was estimated following Mize and Langdon[29]. Vitamin C and vitamin E levels in the liver tissue were determined using the methods of Omaye et al., and Varley et al., respectively[30,31.]

Determination of membrane bound ATPase in liver tissue of rats

Na+/K+ ATPase activity in liver tissue was analyzed according to Bonting[32], while Mg2+ ATPase and Ca2+ ATPase activities were estimated using the methods of Ohnishi et al., and Hjerten and Pan[33,34], respectively. Phosphate liberation was measured using the procedure of Fiske and Subbarow [35].

Histopathological Examination:

A piece of liver tissue was sectioned and placed immediately in 10% neutral buffered formalin and were stained with hematoxylin and eosisn (H & E) for histopathological analysis[36].

Gene Expression Analysis by Real-Time PCR

Total RNA was isolated from tissue samples using a standard protocol involving homogenization with RNA isolation reagent, phase separation with chloroform, and precipitation with isopropanol. The RNA pellet was washed with ethanol and dissolved in Milli-Q water by heating. RNA quantification was

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performed spectrophotometrically, assessing purity via A260/280 ratios. Complementary DNA (cDNA) was synthesized from RNA using reverse transcriptase in a two-step reaction. Chomczynski, P., & Sacchi, N.[37]. Quantitative Real-Time PCR (qRT-PCR) was conducted using gene-specific primers and SYBR Green chemistry, following a three-step thermal cycling process: denaturation, annealing, and extension.

Protein Expression Analysis by Western Blotting

Tissue lysates were prepared by homogenizing cleaned liver samples in RIPA buffer supplemented with protease and phosphatase inhibitors. The homogenates were subjected to sequential centrifugation to obtain clarified protein extracts. The supernatant, containing the protein lysate, was used for downstream Western blot analysis to quantify protein expression by Brown K[38].

Statistical Analysis

The data was subjected to one-way analysis of variance (ANOVA) and Duncan's multiple range test was done to evaluate the significance of differences between the control and treatment groups using a computer based software (Graph Pad Prism version 7). Values are presented as Mean ± S.D. and P value <0.05 was considered significant.

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Results

Table-1 Effect of MSG and CUR on serum AST, ALT and ALP activities in rats.

Groups	AST (U/L)	ALT (U/L)	ALP (U/L)
Group I	36.08 ± 1.9	29.14 ± 1.60	80.37 ± 2.9
Group II	71.8 ± 3.4 ^{a***}	66.05 ± 4.5 ^{a***}	196.7 ± 6.8 ^{a***}
Group III	52.3 ±1.2 ^{a,b***}	50.9 ± 2.27 ^{a***b**}	106 ± 3.97 $^{a**, b***}$
Group IV	43.7 ± 1.6 ^{b***}	41.7 ± 1.4 ^{a*b***}	81.8 ± 2.25 ^{b***c**}
Group V	37.7 ± 2.2	33.5 ± 2.3	78.6 ± 4.92
Group VI	38.98 ± 2.04	31.8 ± 2.6	83.38 ± 4.5

Table-1 Effect of MSG and CUR on serum AST, ALT and ALP activities in rats. The results are expressed as Mean ± S.D. of (n=6). 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.

Table 1 demonstrates the impact of MSG and CUR on serum AST, ALT, and ALP activities in rats. Group II, treated with MSG alone, showed a significant increase in AST, ALT, and ALP activities compared to the control (Group I), indicating hepatic damage due to low dose MSG-induced oxidative stress ***(p<0.001). Co-administration of CUR and SIL in Groups III and IV respectively, resulted in a dose-dependent reduction in these enzymes compared to Group II, with Group III showing moderate improvement (***p<0.001, **p<0.01) and Group IV nearly restoring levels to baseline (***p<0.001, **p<0.01). The results highlight curcumin's hepatoprotective properties, likely due to its antioxidant and anti-inflammatory effects. Groups V and VI,

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treated with CUR alone and SIL alone, displayed enzyme levels comparable to the control, confirming its safety profile. These findings suggest CUR effectively mitigates MSG-induced hepatotoxicity.

Figure-1 Effect of MSG and CUR on liver AST, ALT and ALP in rats

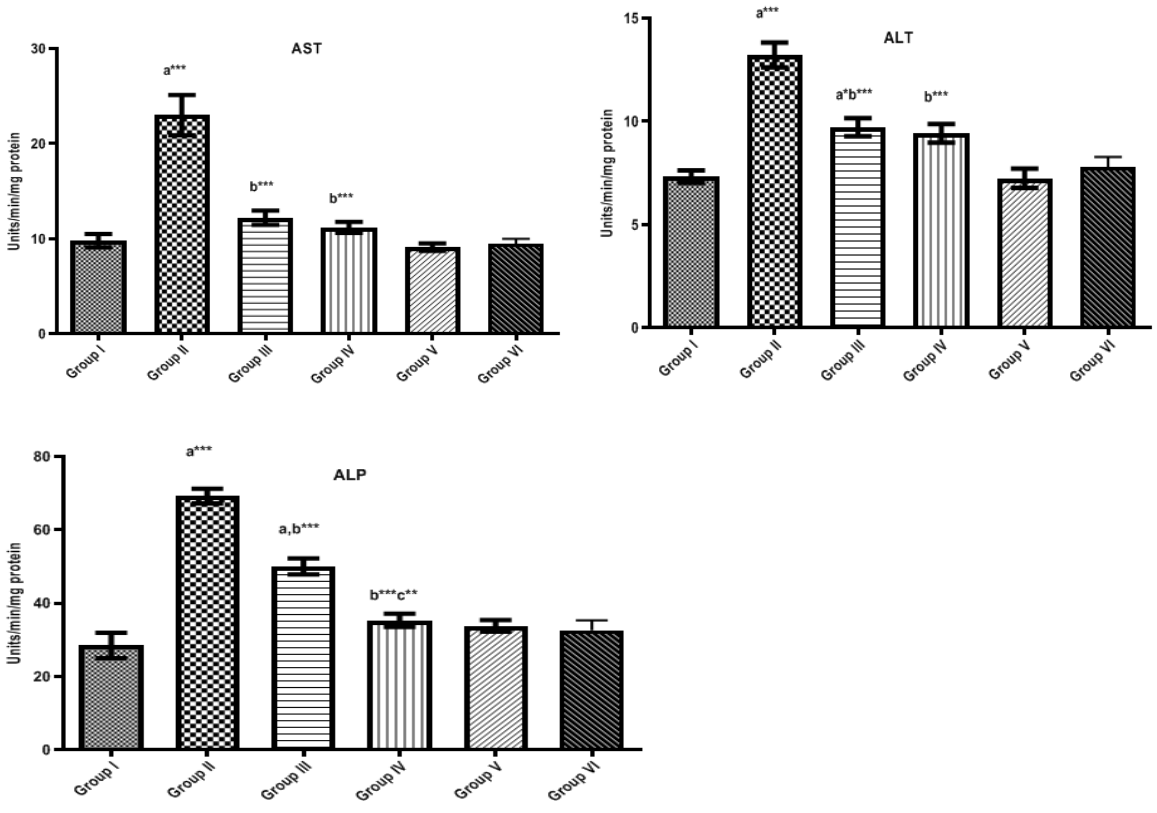


Figure-1 Effect of MSG and CUR on liver AST, ALT and ALP activities in rats. The results are expressed as Mean ± S.D. of (n=6). a. Denotes Group-I compared to Group-II, III, IV, V and VI. b. Denotes Group-II compared to Group-III and IV. c. Denotes Group-III compared to Group-IV. *p<0.05; ** p<0.01; ***p<0.001.

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Figure 1 shows the effect of CUR on marker enzymes of hepatotoxicity in liver tissue, providing evidence of its protective role against liver damage. Group II, treated with MSG, exhibited a significant increase (**p<0.01, ***p<0.001) in marker enzyme levels compared to the control (Group I), reflecting pronounced hepatotoxicity. Co-administration of CUR and SIL in Groups III and IV respectively significantly reduced these elevated enzyme levels, with Group IV showing a more pronounced reduction (**p<0.01, ***p<0.001) than Group III, indicating a dose-dependent hepatoprotective effect. Group V and Group VI, treated with CUR alone and SIL alone, maintained enzyme levels comparable to Group I, confirming Curcumin's safety and non-toxic profile. These findings validate Curcumin's antioxidant and anti-inflammatory properties, effectively mitigating low dose MSG-induced hepatic damage and preserving liver function.

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Figure-2 Effect of MSG and CUR on liver LPO in rats

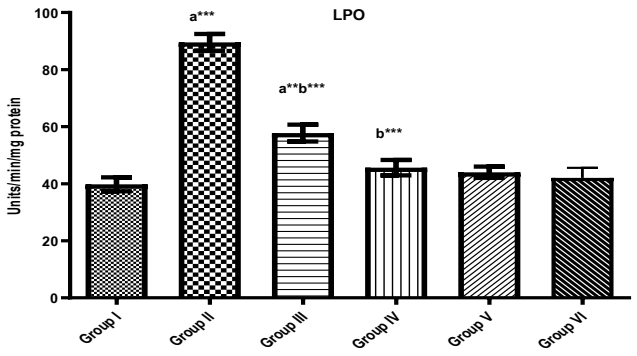


Figure.2. Effect of MSG and CUR on liver LPO in rats. The results are expressed as Mean ± S.D. of (n=6). a. Denotes Group-I compared to Group-II, III, IV, V and VI. b. Denotes Group-II compared to Group-III and IV. **p<0.01; ***p<0.001

Figure 2 depicts the impact of CUR on LPO levels in the liver tissue of rats exposed to MSG. Group II, treated with MSG alone, exhibited a significant increase in LPO levels (***p<0.001) compared to the control (Group I), highlighting oxidative stress-induced hepatic damage. Treatment with CUR and SIL in Groups III and IV resulted in a dose-dependent reduction in LPO levels, with Group IV showing a more pronounced protective effect. Groups V and VI, treated with CUR alone and SIL alone, maintained LPO levels comparable to the control, indicating its safety and inherent antioxidant properties. These results demonstrate Curcumin's ability to counteract low dose MSG-induced

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oxidative damage by reducing lipid peroxidation and replenishing antioxidant defenses in liver tissue.

Table-2 Effect of MSG and CUR on liver SOD, CAT, GPX, GR, and GST in rats

Groups	SOD	Catalase	GST	GPX	GR
Group I	47.14 ± 6.03	37.84 ± 6.69	32.54±2.67	63.34±1.93	30.59±2.19
Group II	19.65 ± 2.83 a***	25.94 ± 4.64 a***	12.61±0.92 a***	28.66±2.69 a***	12.89±0.96 a***
Group III	38.69 ± 8.73 a**	29.99 ± 7.85 a**	19.31±1.10 a**	40.12±2.22 a***	19.57±1.12 a,b***
Group IV	38.88 ± 6.94 a*	41.18 ± 8.33	32.59±3.06 b***c**	57.42±3.97 b*** c**	32.96±3.08 c***
Group V	36.33 ± 6.08 a*	37.31 ± 8.77	34.09±2.24	74.71±3.27	34.52±2.33
Group VI	29.56 ± 5.91 a***	36.86 ± 8.92	35.2±3.56	71.98±3.15	34.54±3.42

Table-2 Effect of MSG and CUR on liver SOD, CAT, GPX, GR, and GST in rats.The results are expressed as Mean ± S.D. of (n=6). 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 illustrates the effect of MSG and CUR on liver antioxidant enzymes, including SOD, CAT, GPx, GR, and GST in rats. Group II, treated with MSG alone, showed a significant reduction in the activity of all these enzymes compared to the control (Group I), reflecting impaired antioxidant defense

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and increased oxidative stress. Co-treatment with CUR and SIL in Groups III and IV restored these enzyme activities in a dose-dependent manner, with Group IV demonstrating a more pronounced improvement, indicating Curcumin's robust antioxidant potential. Groups V and VI, receiving CUR alone and SIL alone, exhibited enzyme activity levels similar to the control group, confirming Curcumin's safety. These findings underscore Curcumin's efficacy in enhancing antioxidant enzyme activities, thereby mitigating low dose MSG-induced oxidative damage in liver tissue.

Table-3 Effect of MSG and CUR on liver Vit-C, Vit-E and GSH in rats

Groups	Vit-C	Vit-E	GSH
Group I	60.14 ± 8.49	13.38 ± 2.20	15.77 0.74
Group II	22.64 ± 5.40 a***	6.00 ± 1.47 a***	8.63 0.42 a***
Group III	43.47 ± 9.08 b**	10.68 ± 1.28 b**	13.23 1.15 b*
Group IV	52.33 ± 8.79 b*	14.46 ± 2.95 b*	13.68 0.48 b*
Group V	60.33 ± 7.37	14.42 ± 2.41	14.41 0.51
Group VI	66.34 ± 7.13	16.08 ± 3.16	14.65 1.27

Table-3 Effect of MSG and CUR on liver Vit-C, Vit-E and GSH in rats. The results are expressed as Mean ± S.D. of (n=6). 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.

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Table-3 demonstrates the levels of **Vit-C, Vit-E and GSH** in the liver tissue of rats treated with MSG and CUR. Group II, treated with MSG alone, showed a significant depletion in the levels of these vitamins and GSH compared to the control (Group I), indicating oxidative stress-induced depletion of essential antioxidants. CUR and SIL co-treatment in Groups III and IV respectively resulted in a dose-dependent restoration of vitamin C, E and GSH levels, with Group IV showing a more pronounced effect. Groups V and VI, treated with CUR alone and SIL alone, maintained levels comparable to the control, confirming the safety and antioxidant properties of CUR. These results emphasize Curcumin's ability to restore endogenous antioxidant vitamins and protect against low dose MSG-induced oxidative stress

Table-4 Effect of MSG and CUR on liver Membrane Bound ATPases in rats

Groups	**$NA^{2+}K^{+}$ ATPase**	**Mg^{2+}ATPase**	**Ca^{2+} ATPase**
Group I	4.58±0.22	1.21±0.05	1.42±0.08
Group II	$1.74\pm0.12^{a***}$	$0.450.07^{a***}$	$0.59\pm0.04^{a***}$
Group III	$3.21\pm0.21^{a,b***}$	0.96±0.04	$1.02\pm0.07^{a***b**}$
Group IV	$4.28\pm0.23^{b***c**}$	$1.27\pm0.07^{b***c*}$	$1.33\pm0.04^{b***c**}$
Group V	4.43±0.19	1.43±0.08	1.58±0.06
Group VI	4.96±0.17	1.36±0.04	1.47±0.02

Table-4 Effect of MSG and CUR on liver Membrane Bound ATPases in rats. The results are expressed as Mean ± S.D. of (n=6). 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.

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Table-4 highlights the activity of membrane-bound ATPases, crucial for maintaining ionic balance and cellular homeostasis in the liver. Group II, exposed to MSG alone, exhibited a significant reduction in ATPase activities compared to the control (Group I), indicating compromised membrane integrity and function due to oxidative stress. CUR and SIL co-treatment in Groups III and IV significantly restored ATPase activities in a dose-dependent manner, with Group IV showing the highest recovery. Groups V and VI, treated with CUR alone and SIL alone, showed ATPase activities similar to the control, affirming Curcumin's non-toxic nature. These findings suggest that CUR protects against low dose MSG-induced disruptions in membrane-bound ATPases, preserving cellular homeostasis and liver function.

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Figure-3 Effect of MSG and CUR on Nrf2 Protein Expression in rats.

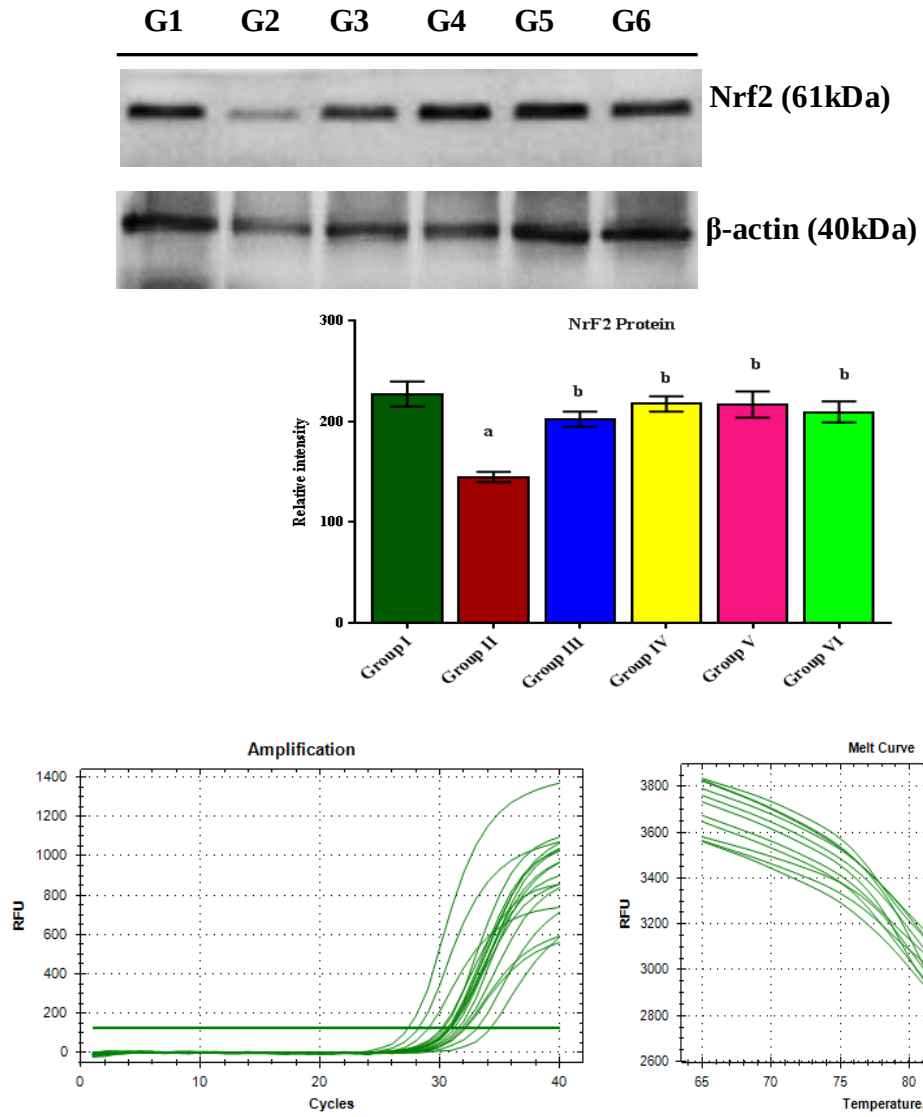


Figure-3 Effect of MSG and CUR On Nrf2 Protein Expression in Rats. Each bar represents Mean ± S.E.M of 6 animals. a-compared to control; b-compared to MSG induced toxicity. Significance at the levels of ***p<0.05**

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Figure-3 demonstrates the influence of CUR on the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) protein, a critical regulator of cellular antioxidant defenses, in liver tissue. Group II, treated with MSG alone, showed a significant downregulation of Nrf2 expression compared to the control (Group I), reflecting suppressed antioxidant signaling and increased vulnerability to oxidative stress. Co-treatment with CUR and SIL in Groups III and IV significantly enhanced Nrf2 protein expression in a dose-dependent manner, with Group IV displaying the highest induction of Nrf2. This restoration suggests Curcumin's ability to activate antioxidant pathways and counteract low dose MSG-induced toxicity. Groups V and VI, treated with CUR alone and SIL alone, maintained Nrf2 expression levels comparable to the control group, indicating its safety and potential as a natural antioxidant. These results highlight Curcumin's role in modulating Nrf2 expression to mitigate oxidative damage in the liver.

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Figure-4. Effect of MSG and CUR on Histopathology of liver tissue of experimental animals (×40)

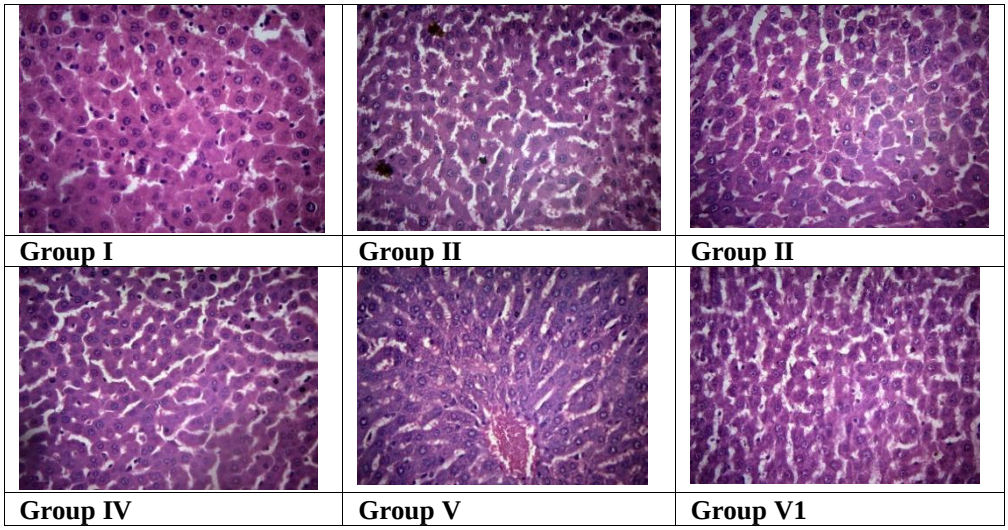


Figure-4 Effect of MSG and CUR on Histopathology of liver tissue of control and experimental animals (×40)

Figure-4 presents the histopathological examination of liver tissue from experimental animals, highlighting the effects of chronic low dose exposure of MSG and CUR on liver morphology. Group I, the control group, showed normal liver architecture with well-defined hepatocytes and intact lobular structure. Group II, treated with MSG alone, exhibited severe liver damage, including hepatocellular degeneration, necrosis, and inflammatory cell infiltration, indicative of MSG-induced hepatotoxicity. Group III and

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Group IV, receiving MSG with CUR and SIL treatment, displayed a dose-dependent improvement, with Group IV showing near-normal liver morphology, suggesting that CUR mitigates MSG-induced liver damage by preserving cellular integrity and reducing inflammation. Group V and Group VI, treated with CUR alone and SIL alone, showed healthy liver tissue with no apparent histological alterations, confirming the safety of CUR. These histopathological findings correlate with the biochemical results, supporting Curcumin's hepatoprotective effects against MSG-induced toxicity. The comprehensive analysis of these results demonstrates the significant hepatoprotective effects of both CUR and SIL, against low dose MSG-induced oxidative stress and liver damage, with both treatments showing comparable efficacy in restoring normal hepatic function and structure.

Discussion

Oxidative stress is a hallmark of low dose MSG chronic exposure -induced hepatotoxicity, driven by excessive reactive oxygen species (ROS) production and depletion of antioxidant defenses[39,40]. A plethora of research studies in experimental animals have proved the association between oxidative stress and hepatototoxicity. Finding a promising hepatoprotective and antioxidant agent that can curb the deletarious effects of chronic low dose MSG is the need of the hour. Research shows that there is a growing interest in

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the use of phytochemicals to study the hepatoprotective and antioxidant effects against chronic exposure of low dose MSG induced hepatic damage. In the current study we evaluated the hepatoprotective and antioxidant properties of CUR against chronic low dose exposure of MSG-induced oxidative stress and liver damage in male wistar albino rats. The findings highlighted curcumin's ability to counteract the deleterious effects of low dose MSG, primarily through its potent antioxidant and anti-inflammatory mechanisms.

Low dose chronic exposure of MSG induced hepatic damage is confirmed by a marked elevation in the activities of the serum and liver AST, ALT and ALP showing its hepatotoxic potential. The increase in the levels of marker enzymes is due to the extensive damage to the structural integrity of the liver causing these cytoplasmic enzymes to be released into systemic circulation. Low dose MSG toxicity also leads to the generation of ammonium ions and Reactive Oxygen Species (ROS) which then binds to poly unsaturated fatty acids which damages plasma and mitochondrial membranes causing release of these hepatic marker enzymes into serum. In this study, CUR significantly prevented the chronic low dose exposure of MSG induced elevation in the hepatic marker enzymes by maintaining structural integrity and inhibiting release of these enzymes, which suggested its hepatoprotective properties.

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Administration of low dose MSG on chronic exposure in experimental animals have shown to increase the oxidative stress markers LPO, and decrease enzymic and non enzymic antioxidants GSH, SOD, CAT, GPX, GR, and GSH in liver tissue. Our results are in agreement with these studies. CUR supplementation significantly enhanced the activity of key antioxidant enzymes like SOD which neutralizes superoxide radicals, CAT essential for decomposing hydrogen peroxide into water and oxygen, GPx which utilizes reduced glutathione (GSH) to detoxify peroxides indicating its role in mitigating ROS overload. These results highlight Curcumin's ability to restore antioxidant homeostasis and reduce oxidative stress[41,42]. Vit-C and Vit-E, critical non-enzymatic antioxidants, exhibited significant improvements following CUR treatment. These vitamins play a vital role in neutralizing lipid peroxidation and stabilizing cell membranes. Increased levels of these antioxidants in CUR treated animals align with findings in other oxidative stress models, supporting the compound's efficacy in enhancing the body's natural defense systems. By preventing lipid peroxidation, CUR effectively protected hepatic cellular integrity, reducing damage caused by ROS and peroxides[11,43]. All the membrane bound ATPases activities significantly declined on chronic low dose MSG treatment and the CUR and SIL treatments effectively reversed the changes to normalcy indicating their membrane stabilizing properties. Decline

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in status of these enzymes further concretely confirms the oxidative stress and hepatotoxicity induced by chronic low dose exposure of MSG.

This study comparison between CUR and SIL revealed that Curcumin's protective effects were often on par with or exceeded those of SIL. SIL is a gold standard for hepatoprotection due to its ability to stabilize cell membranes, enhance protein synthesis, and scavenge free radicals[44]. However, Curcumin's dual action as a direct antioxidant and modulator of cellular stress responses likely explains its comparable efficacy. Moreover, Curcumin's potential advantages include its anti-inflammatory and anti-apoptotic effects, as demonstrated in other liver injury models[45].

Nrf2 signaling pathway has been shown to play a key role in cellular protection against oxidative stress. The activation of Nrf2 protein expression in turn induces many other antioxidant genes and helps curbing the oxidative stress and enhances the antioxidant defense system and contributes to its protective role. the The mechanistic basis of Curcumin's hepatoprotective action lies in its ability to modulate the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway, enhancing the transcription of antioxidant enzymes. It also suppresses pro-inflammatory pathways, such as NF-κB, thereby reducing cytokine-induced liver damage[46]. The observed reductions

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in lipid peroxidation and improvements in antioxidant capacity affirm Curcumin's therapeutic potential for managing MSG-induced liver dysfunction. These findings pave the way for further investigations into Curcumin's application in clinical settings, particularly as a dietary supplement for individuals at risk of oxidative liver damage[47].

Our study demonstrates Curcumin's significant protective effects against MSG-induced oxidative stress and hepatotoxicity. The present study provides evidence that chronic exposure to low-dose monosodium glutamate induces hepatotoxicity, characterized by oxidative stress, disruption of membrane ATPase activity, altered Nrf2 gene expression, and histopathological changes. Conversely, curcumin exerted significant hepatoprotective effects, comparable to those of silymarin, by mitigating oxidative stress, restoring membrane ATPase activity, modulating Nrf2 gene expression, and improving histopathological alterations. These findings suggest that curcumin may be a viable therapeutic agent for ameliorating MSG-induced hepatotoxicity, and warrant further investigation into its clinical efficacy and safety.

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