# Anti-oxidant and Hepatoprotective Possibilities of Lycopene against Monosodium Glutamate Induced Detrimental Effects in Rats

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**Abstract:**

The present experiment aimed to investigate anti-oxidant and hepatoprotective possibilities of lycopene (LYC) versus hepatic biochemical alterations induced by administration of monosodium glutamate (MSG). Rats were classified into five groups; Group I- (control), Group II- (MSG 15 mg/kg ), Group III- (MSG 35 mg/kg), Group IV- (MSG 15 mg/kg + LYC), Group V- (MSG 35 mg/kg + LYC). Our results demonstrated that MSG administration at both doses (15, 35 mg/kg /day) for 30 days induced hepatic toxicity as indicated with elevated hepatic enzyme leakage, oxidative stress, and hepatic histopathological deterioration comparing to control group. On the contrary, supplementation of LYC (10 mg/kg /day) pre- MSG administration for 10 days and co-administration with MSG for 30 days partially restored hepatic enzymes and elevated the anti-oxidant enzyme activities via reducing hepatic enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST) and increasing superoxide dismutase (SOD), glutathione peroxidase (GPx) activities, reduced glutathione (GSH) level, in line with decreased malondialdehyde (MDA), and transforming growth factor beta1 (TGF-β1). As well as, lycopene administration improved hepatic architecture comparing to MSG. Taken together, the present results summarize that lycopene administration showed hepatoprotective effects versus monosodium glutamate promoted hepatic toxicity and thus can be considered as a novel hepatoprotective medication in clinic after being valid.

**Key words**: Monosodium glutamate, Lycopene, Liver, Oxidative stress, Rats

**Introduction**: Monosodium glutamate (MSG)

(E621), the sodium salt of L-glutamic acid, is widely utilized as flavor enhancer of food to generate umami taste ***(Zanfirescu et al., 2019)***. MSG presents in many different ingredients and processed foods such as crackers, salad dressings, meat, and frozen dinners from market and restaurants ***(Niaz et al., 2018).*** MSG-supplemented rats displayed raised fasting blood glucose and obesity, with time it developed type-2 diabetes ***(Morrison et al., 2008; Bousova et al., 2016)***. MSG–obese adult rats evoked metabolic syndrome characterized by dyslipidemia, abdominal obesity, glucose intolerance, insulin resistance, hypertension and non-alcoholic steatohepatitis (NASH) ***(De Oliveira et al., 2011)***. Additionally, daily MSG oral administration (60 mg/kg) to mature male rats for 4 weeks induced hepatotoxic effects ***(Diab and Hamza, 2016)***. MSG administration (6 mg/g/day) to rats, per os (p.o), for 45 days resulted in testicular oxidative stress and apoptosis ***(Sarhan 2018).*** Also, MSG administration caused renal toxicity ***(Sharma, 2015)***, male reproductive dysfunction ***(Kayode et al., 2020)*** and neurotoxic effects ***(Gürgen et al., 2021).*** It increased brain lipid peroxidation, nitric oxide, 8-OHdG, accumulation of ß-amyloid, whereas decreased glutathione, superoxide dismutase, and catalase ***(Saher, 2017; Liao et al., 2020)***. These toxic side effects may occur because MSG triggered biochemical alterations; oxidative stress, apoptosis, fibrosis ***(Albrahim and Binobead, 2018)***. Several active components and essential oils commonly available in plants are strongly considered as good natural anti-oxidants. Many studies regarded these plants, their oils and extracted active components as proper alternatives to synthetic anti-oxidants ***(Inanc Horuz and Maskan, 2015).*** Lycopene (LYC) is an acyclic carotenoid (a derivative of vitamin A) which causes red coloring of various vegetables and fruits including tomato, watermelon, guava, and grapefruits ***(Rao et al. 2006)***. It is famous for its anti-oxidant properties ***(Palozza et al., 2010)***. Several experiments have reported that lycopene evoked anti-oxidant, anti-inflammatory ***(Wang et al., 2010),*** immunomodulatory ***(Eze et al. 2019)***, anti-hepatic steatosis ***(Chen et al., 2019),*** antidiabetic, and anti-obesity possibilities ***(Zhu et al., 2020).***

## Material and Methods:

### Rats' management and housing

The current study was conducted on a total number of 35 healthy male Wistar albino rats weighting 130-180 gm. Rats were housed in

plastic cages under 12:12 h. natural light/ dark cycle with free access to basal diet and water kept in specific opened containers confined in the cages. They were fed standard balanced ration according to ***Becker et al. (2016)***. Rats were kept for 2 weeks accommodation prior to the onset of the study. The experimental protocol was accepted and approved by the Research Ethical Committee of Faculty of Veterinary Medicine, Suez Canal University, Egypt.

**Chemicals:**

a) Monosodium glutamate (MSG) is a white powder supplied by Sinochem Lianyungang Co. China.

b) Lycopene (LYC) is a red colored liquid manufactured by NOW FOODS Co., USA.

**Experimental Design**

Rats were randomly allocated into 5 experimental groups 7 rats each; Group I- (control): Rats had free access to food and water. Group II- (MSG 15 mg): Rats received MSG 15 mg/kg daily by oral gavage for one month ***(Abdel-Reheim et al., 2014)***. Group III- (MSG 35 mg): Rats received MSG 35 mg /kg daily by oral gavage for one month ***(Elbassuoni et al., 2018)***. Group IV- (MSG 15 mg + LYC): Rats received LYC 10 mg/kg daily by oral gavage ***(Jiang et al., 2016)*** for 10 days, then administered MSG 15 mg/kg in combination with LYC for one month. Group V- (MSG 35 mg + LYC): Rats received LYC 10 mg/kg by oral gavage for 10 days, then administered MSG 35 mg/kg in combination with LYC for one month. Both MSG and LYC were dissolved in saline and corn oil, respectively prior to their oral administration.

At end of the experiment, after overnight fasting, each rat was euthanized under xylazine effect. Blood was collected from eye medial canthus using micro hematocrit tubes. Blood was taken into a dry clean screw-capped centrifuge tubes, allowed to clot at room temperature, followed by centrifugation at 3000 r.p.m. for 15 minutes period in order to separate clear serum samples that furtherly used for biochemical parameters estimation. Animals were sacrificed via cervical decapitation and liver from each rat was carefully dissected. Liver tissues were divided into two parts. One part was homogenized in phosphate-buffered saline (PBS, pH = 7.4) by Teflon homogenizer (Glass-Col homogenizer system). Next, the homogenate was transferred into a centrifuge set at 1500 xg for 15 min. After that, supernatant was collected and kept at -20 $^{o}$C for assessment of oxidative stress. Another part was fixed using 10% neutral buffered formalin then prepared for

histopathology.

**Biochemical parameters estimation:**

**Measurement of serum liver function enzymes activity:**

Determination of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities were conducted using the kits of spectrum, Cairo, Egypt according to manufacturer's instructions.

**Determination of hepatic oxidative stress markers:**

Hepatic superoxide dismutase (SOD), glutathione peroxidase (GPx), reduced glutathione (GSH), and malondialdehyde (MDA) were measured calorimetrically using kits of (Biodiagnostic, Egypt). Transforming growth factor beta 1 (TGF-β1) was estimated via rat TGF beta 1 sandwich enzyme-linked immunosorbent assay (ELISA) kit (MyBiosource Cataloge# MBS824788). All assay procedures were done in accordance with the manufacturer's instructions.

**Statistical Analysis:**

Data of the present study were analyzed using randomized complete design *Analysis of Variance* (RCD-ANOVA) procedures for testing of significance among groups followed by *Duncan's* multiple range test. Statistical analysis was carried out by using SPSS version 25 for windows (SPSS Inc., Chicago, USA). Data were expressed as Mean ± SE and considered significant at a probability level of 0.05 for each ($P < 0.05$).

**Results:**

**Effect of Lycopene supplementation on hepatic enzymes activities in monosodium glutamate administered rats**

Monosodium glutamate administration significantly ($P < 0.05$) increased ALT and AST activities comparing to control. On contrary, lycopene supplementation minimized hepatic enzymes leakage comparing to monosodium glutamate administered rats.

**Effect of Lycopene supplementation on hepatic oxidative stress status in monosodium glutamate administered rats**

Monosodium glutamate administration significantly ($P < 0.05$) decreased hepatic SOD, GPx activities, and GSH level whereas increased MDA and TGF-β1 levels. Lycopene supplementation with MSG partially ameliorated these markers indicating that it induced hepatoprotective, anti-oxidant, and antifibrosis impact.

**Histopathological investigation**

Hepatic section of control group showed preserved architecture within lobules. Hepatocytes appeared as radiating cords

surrounding the central vein, with patent biliary sinusoids. Uniform portal tract is evident. On the other hand, hepatic section of MSG (15mg/kg) group showed congestion in central vein. Most of portal tracts were moderately expanded with fibrous tissue, and chronic inflammation. Additionally, hepatic section of MSG (35mg/kg) group revealed significant macro-vesicular steatosis, involving more than 50% of hepatocytes. There were scattered foci of drop-out hepatocytes and replacement with inflammatory cells (lobulitis). Some portal tracts were mildly expanded with chronic inflammatory cells. Interestingly, hepatic section of MSG (15mg/kg) + LYC group showed only slight congestion in portal vessels and mild hydropic degeneration. As well as, hepatic section of MSG (35mg/kg) + LYC group displayed congestion in central vein. Most of portal tracts were mildly expanded with fibrous tissue, with mild chronic inflammation and proliferated bile ductuli.

**Table 1.** *Effect of Lycopene supplementation on hepatic enzymes activities in monosodium glutamate administered rats.*

| Marker | Control | MSG 15 mg | MSG 35 mg | MSG 15 mg + LYC | MSG 35 mg + LYC |
|---|---|---|---|---|---|
| **ALT (U/L)** | 21.00 ±1.70 [d] | 34.80 ±2.49 [b] | 45.60 ±2.65 [a] | 28.00 ±1.92 [c] | 38.20 ± 1.52 [b] |
| **AST (U/L)** | 30.80 ±2.55 [d] | 47.00 ±2.30 [b] | 61.40 ±2.29 [a] | 38.20 ±2.15 [c] | 41.80 ±2.20 [c] |

Each value represents mean ± SE for 7 rats in each group.
Values with different superscript differ significantly at $p<0.05$

**Table 2**. *Effect of Lycopene supplementation on hepatic superoxide dismutase (SOD), glutathione peroxidase (GSH-px) activities, glutathione (GSH), malondialdehyde (MDA) and transforming growth factor beta1 (TGF-β1) levels in monosodium glutamate administered rats.*

| Marker | Control | MSG 15 mg | MSG 35 mg | MSG 15 mg + LYC | MSG 35 mg + LYC |
|---|---|---|---|---|---|
| **SOD (U/g tissue)** | 3.61 ±0.08 [a] | 2.68 ±0.23 [b] | 2.22 ±0.28 [b] | 2.81 ±0.25 [b] | 2.36 ±030 [b] |
| **GPx (U/ g tissue)** | 111.20 ±4.63 [a] | 89.40 ±5.67 [c] | 68.60 ±4.30 [e] | 97.60 ±3.8 0 [b] | 80.00 ±4.84 [d] |
| **GSH (mmol/g tissue)** | 2.17 ±0.05 [a] | 1.91 ±0.04 [c] | 1.66 ±0.04 [d] | 2.01 ±0.04 [b] | 1.74 ±0.02 [c] |
| **MDA (nmol/g tissue)** | 13.20 ±1.39 [d] | 26.60 ±1.56 [b] | 36.40 ±3.0 [a] | 21.40 ±1.40 [c] | 31.40 ±1.96 [b] |
| **TGF-β1 (pg/g tissue)** | 117.80 ±4.83 [d] | 142.40 ±4.04 [c] | 180.60 ±3.64 [a] | 133.20 ±3.83 [c] | 169.60 ±3.23 [b] |

Each value represents mean ± SE for 7 rats in each group.
Values with different superscript differ significantly at $p<0.05$

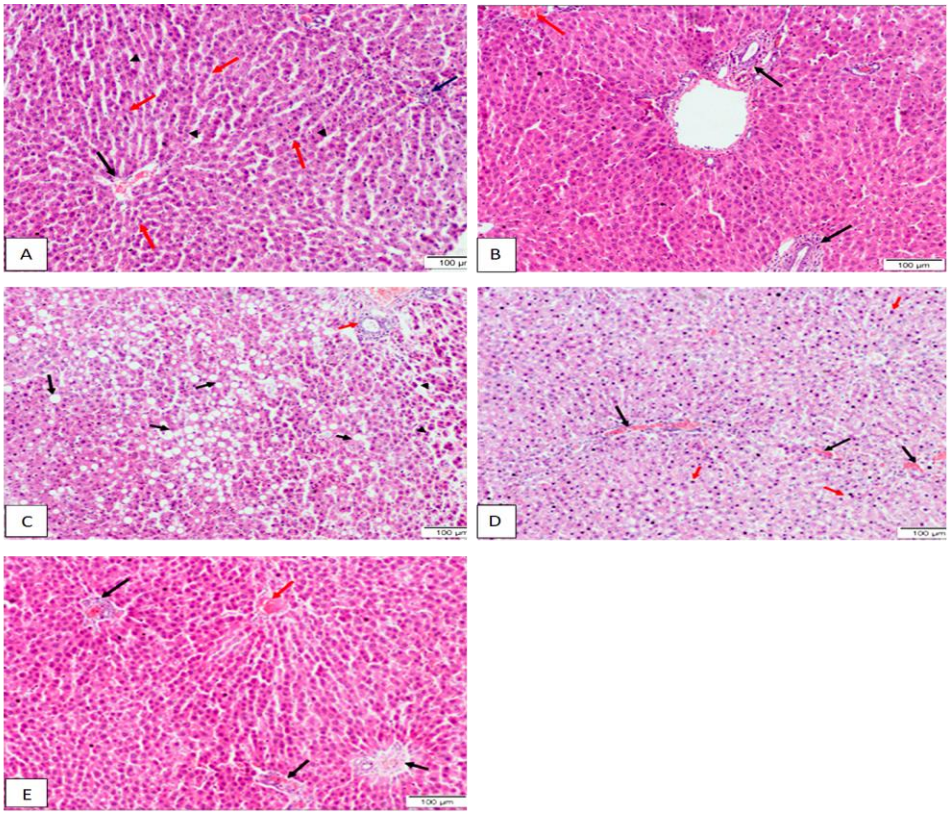


**Figure 1:** *Photomicrographs of liver sections from rats treated with lycopene against monosodium glutamate induced hepatic toxicity (H&E) revealing:*

**A:** hepatic section of control group showed preserved architecture within lobules, with central vein (black arrow), radiating from it cords of uniform hepatocytes (red arrows), and patent biliary sinusoids (arrow heads). Uniform portal tract is evident (blue arrow). **B:** hepatic section of MSG (15 mg/kg) group showed congestion in central vein (red arrow). Most of portal tracts were moderately expanded with fibrous tissue, and chronic inflammation (black arrows). **C:** hepatic section of MSG (35 mg/kg) group showed significant macro-vesicular steatosis, involving more than 50% of hepatocytes (black arrows). There were scattered foci of drop-out hepatocytes and replacement with inflammatory cells (lobulitis) (arrow heads). Some portal tracts were mildly expanded with chronic inflammatory cells (Red arrow). **D:** hepatic section of MSG (15mg/kg) + LYC group showed portal tracts only with congested vessels (black arrows). Hepatocytes showed mild hydropic degeneration (red arrows). **E:**

hepatic section of MSG (35mg/kg) + LYC group showed congestion in central vein (red arrow). Most of portal tracts were mildly expanded with fibrous tissue, with mild chronic inflammation and proliferated bile ductuli (Black arrows).

**Discussion:**

Liver is considered the most vulnerable body organ to oxidative damage due to its high oxidizable substances content ***(Li at al., 2015)***. Upon destruction of hepatic cellular membrane, several cytosolic enzymes are liberated into general circulation thus elevating their levels in blood stream ***(Etim et al., 2006; Pari and Suresh, 2008)***. Consequently, elevation of serum ALT and AST activities may reflect degeneration of hepatic cells due to the increased cell membrane permeability or cellular necrosis. The amount of released liver enzymes directly corresponds to severity of liver damage ***(El-Khayat et al., 2009)***. In the present study, MSG induced hepatic toxicity that is evidenced by increased serum ALT and AST activities in comparison to the normal control agreeing with ***Al-Mamary et al. (2002)*** and ***Ortiz et al. (2006)***. This may be attributed to the fact that MSG can easily dissociate into sodium and L-glutamate which is then converted to glutamine. Accumulation of glutamine in liver cells results in their deterioration; accordingly, liberation of ALT and AST enzymes with elevation of their activities in blood ***(Pari and Suresh, 2008)***. Moreover, deamination of glutamine, released from MSG dissociation, results in ammonium ($NH_4^+$) ion overload which could also induce hepatic injury leading to increased ALT and AST activity ***(Ortiz et al. 2006).*** These findings were proved by the significant ($P < 0.05$) decreased hepatic GSH level, SOD, GPx activities in line with elevated MDA, and TGF-β1 in this group. These findings came in agreement with those of ***Pavlovic et al. (2007)*** and ***Elbassuoni et al. (2018)***. MSG has the ability to promote reactive oxygen species (ROS) production since glutamate induces elevation of α-ketoglutarate dehydrogenase enzyme activity, a likely generator of ROS. Furthermore, intracellular aggravation of calcium via glutamate receptors may invigorate free radical generation as well as inhibit uptake of cystine causing depression of GSH levels thus promoting hepatic oxidative stress ***(Sharma, 2015)***. Oxidative stress is generated from depletion of anti-oxidant system that scavenge ROS. Whilst SOD converts superoxide radicals into

hydrogen peroxide, CAT catalyzes the conversion hydrogen peroxide to water. GPx uses GSH to reduce hydrogen peroxide into water. Hence, alterations in anti-oxidant defense systems leads to lipid peroxidation and production of MDA ***(Honma et al., 2020)***.

Many researchers have proposed that oxidative stress can induce the release of TGF-β1, a key profibrogenic cytokine, which consequently promotes Smad signaling pathway. This results in activation of hepatic stellate cells and collagen production which eventually lead to hepatic fibrogenesis ***(Badr et al., 2019)***. This picture is confirmed by histopathological findings of this group which revealed the hepatocytic response after MSG exposure as proliferation of biliary duct, focal infiltration by inflammatory cells, and fibrosis specially in the higher dose (35 mg/kg /day).

Lycopene evoked anti-oxidant properties as indicated by increased hepatic anti-oxidant enzymes and decreased lipid peroxidation and fibrosis. These may be attributed to its strong anti-oxidant and free-radical scavenging abilities (13.3 times higher than that of α-tocopherol) ***(Müller et al., 2011)***, besides 1,1-diphenyl-2-picrylhydrazyl (DPPH) scavenging potential ***(Bhat et al., 2020)***. Our findings agree with many previous researches. Oral lycopene supplementation has been found to counteract iron-induced hepatic oxidative stress, increased lipid peroxidation, and autophagy in rats ***(Liu et al., 2013).*** Also, pretreatment of rats with tomato pastes orally for 4 weeks in doses equivalent to using LYC at 0.5 and 2.5 mg/kg BW/day has been proved to increase hepatic SOD, glutathione reductase, catalase, and decreased leucocytic DNA damage in N-nitrosodiethylamine-induced oxidative stress ***(Kujawska et al., 2014)***. Additionally, lycopene administration (10 mg/kg p.o) has been reported to increase brain glutathione S-transferase, SOD, catalase activities and glutathione content, and downregulate pro-apoptotic Bax whereas upregulate the anti-apoptotic Bcl-2 in MSG-challenged rats ***(Sadek et al., 2016)***. Moreover, ***Rovero Costa et al. (2019)*** reported that daily oral LYC 20 mg/kg supplementation increases hepatic SOD, catalase, and GPx in non-alcoholic fatty liver disease model in rats. Furthermore, ***Dong et al. (2019)*** has indicated that pretreatment with lycopene in LPS-induced liver injury significantly decreases levels of ALT, AST, lessened MDA content, beside increasing serum SOD activity, and nuclear factor-erythroid 2 related factor 2

(Nrf2) gene expression. This can explain the decreased liver transaminase enzymes and restoration of hepatocytes plasma membranes integrity which is affirmed with the histological outcomes where mild hydropic degeneration and mild fibrosis were observed in lycopene treated groups.

**Conclusion:**

It may be concluded from the current study that monosodium glutamate administration by high doses can cause harmful impact on liver health affecting anti-oxidant system. Supplementation of lycopene have promising cytoprotective powers against hepatic toxicity induced by monosodium glutamate.

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# الليكوبين كمضاد للأكسدة و وقائي للكبد ضد الآثار الضارة التي يسببها الجلوتامات أحادي الصوديوم في الجرذان

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هدفت التجربة الحالية إلى دراسة الإمكانيات المضادة للأكسدة والوقاية للكبد من الليكوبين (LYC) ضد التغيرات الكيميائية الحيوية الكبدية الناجمة عن إعطاء الجلوتامات أحادي الصوديوم (MSG). تم توزيع الجرذان إلى خمس مجموعات ؛ المجموعة الأولى - (المجموعة الضابطة) ، المجموعة الثانية - (15 ملجم MSG / كجم من وزن الجسم) ، المجموعة الثالثة (35 ملجم MSG / كجم من وزن الجسم) ، المجموعة الرابعة - (15 ملجم MSG / كجم من وزن الجسم + LYC) ، المجموعة الخامسة (35 ملجم MSG / كجم من وزن الجسم + LYC). أظهرت النتائج أن إعطاء MSG بكلا الجرعتين (15، 35 ملجم / كجم من وزن الجسم / يوم) لمدة 30 يومًا تسبب في حدوث تسمم كبدي كما يتضح من ارتفاع تسرب الإنزيم الكبدي والإجهاد التأكسدي والتدهور المرضي الكبدي مقارنة بالمجموعة الضابطة. على العكس من ذلك، فإن إعطاء 10 ملجم LYC / كجم من وزن الجسم / اليوم) قبل تعرض الجرذان للجلوتامات أحادي الصوديوم لمدة 10 أيام و كذلك الإعطاء المشترك مع MSG لمدة 30 يومًا يعيد جزئيًا الإنزيمات الكبدية ويزيد من أنشطة الإنزيمات المضاد للأكسدة و ذلك عن طريق تقليل أنشطة الإنزيمات الكبدية الناقلة للأمين (الانين امينوترانسيفريز ALT واسبرتات امينوترانسيفريز AST )، وزيادة أنشطة كلا من سوبر أكسيد ديسميوتاز و جلوتاتيون بيروكسيداز (SOD and GPx) و كذلك مستوى الجلوتاثيون المختزل (GSH)، بما يتماشى مع نقص معامل أكسدة الدهون (MDA)، و عامل النمو المحول- بيتا (TGF-β1). بالإضافة إلى ذلك، إعطاء الليكوبين أدى إلى تحسين البنية الكبدية مقارنة بمجموعة MSG. تلخص النتائج الحالية أن إعطاء الليكوبين له تأثير واقي للكبد ضد سمية الجلوتامات أحادي الصوديوم، وبالتالي يمكن اعتباره دواءً إكلينيكياً جديدًا لوقاية الكبد بعد أخذ التصاريح القانونية اللازمة.