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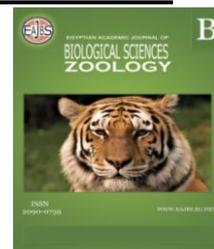


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Therapeutic Role of Nanocurcumin Versus Monosodium Glutamate Toxicity

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ABSTRACT

The use of Nanoparticles (NPs) and nanostructured materials (NSMs) consider a new light in the progress of disease-modifying treatments for many pathological disorders. The present study is an attempt to investigate the curative effect of Nanocurcumin against long-term MSG-administration on rat liver. A total of 40 adult male Wistar albino rats were divided into the following groups: Control group (C) of 14 rats given saline; Nanocurcumin (Nano-Cur) control group of 14 rats inoculated orally with Nano-Cur (100mg/Kg b.wt/day)for 8 weeks; Monosodium group received MSG 10 mg/kg /b. w. for eight weeks; the therapeutic group was first given MSG alone for 4 weeks and was secondly administered Nano-Cur for 4 weeks. At the end of 8 weeks, animals were sacrificed by ether inhalation anesthesia where blood and liver tissues were collected to study biochemical parameters. MSG administration exerted significant elevation of cholesterol, TG, HDL, LDL, VLDL and MDA. Also showed an increase in liver enzymes. On the other hand, in the therapeutic group, Nano-Cur showed significant improvement in the previous parameters.

INTRODUCTION

Additives are natural or artificial substances used for many years for many purposes (taste, flavour, preserve, mix and colour foods) to improve the nutritional value of food like vitamin C and A or to improve palatability such as ascorbic acid and sodium nitrite Hajihasani, M.M., *et al.* (2020).

The food additives are divided into five main categories according to their function such as taste enhance, antioxidants, preservation, stabilizers and colouring agents Hajihasani, M.M., *et al.* (2020).

Monosodium glutamate (MSG) is one of the most ordinally used flavouring agents all over the world which is taken as part of processed food. It gives enhancing capacities like normally happening free glutamate which differ from the four exemplary preferences Hajihasani, M.M., *et al.* (2020), Egbuonu, A.C.C., *et al.* (2010) and Thomas.M and George.S. (2010).

MSG is a broadly used flavour-enhancing food additive that may be present in packed foods without appearing on the label. This might lead to accidentally consumption of MSG above to normal average daily intake of 1.0 g in enlightened

society Zedan, A.M.G, *et al.* (2017).

In spite of its delicious taste and affected appetite enhancement, many studies reported that MSG is toxic to humans and experiment animals Acar.A. (2020). Numerous amounts of free radicals are generated by MSG that can destroy neurons, other tissues and organs (kidney, liver, spleen, CNS, testes and had a genotoxic effect Atef.H. *et al.* (2019).

It causes an increase in oxidative stress and considers the main factor for the initiation of heart diseases and atherosclerosis Singh. K and Ahluwalia. P (2012). Fast foods play an extremely important role in diet-related disorders and metabolites. Overfeeding of tasty and delicious food may cause an impossible intake of nourishment essential for growth and the maintenance of life Diab, A.A, and Hamza, R.Z. (2016).

A large amount of glutamate acid is transmitted during intestinal absorption and eventually, alanine levels are also elevated in the blood of the portal vein Atef, H. *et al.* (2019). Moreover, this elevation leads to increased hepatic metabolism of glutamate, resulting in the release of glucose, lactate, glutamine and other amino acids into circulation.

Moreover, MSG was administrated to adult males resulting in a significant increase in serum cholesterol, LDL- cholesterol and decrease in triglyceride and HDL - cholesterol of monosodium glutamate treated rats compared to the control group Tawfek, N. S., *et al.* (2015) and Helal, E.G.E., *et al.* (2019).

Antioxidants are biological substances that can prevent cell damage caused by free radicals action Kasote, D.M., *et al.* (2015). They have the power to scavenge free radicals which play a very important role in a decreased risk of different diseases such as cardiovascular disease (CVD), diabetes and cancer Gulcin,I. (2020).

One of these antioxidants is curcumin which is a vital component separated from the rhizomes of *C. longa* Heger, M. *et al.* (2014).

Curcumin (Cur), one of the most important herbs comes from the herb *Curcuma longa*'s rhizome which is the main component part of turmeric. Several studies demonstrated that Cur has anti-virus, anti-cancer, antibacterial and anti-inflammatory properties Giannitrapani, L. *et al.* (2014).

Also, the recent studies on experimental animals improved the ability of cur to be absorbed and reached its target organs Ipar, V.S., *et al.* (2019).

The usage of nanoparticles has arisen as a quickly developing area for the safe delivery of several therapeutic agents in many pathological managements, including liver ailments Giannitrapani, L. *et al.* (2014).

MATERIALS AND METHODS

Forty male adult albino Wistar rats the medical research center, Faculty of Medicine, Ain Shams University. Their weights are between 120-180 g representing 4 weeks of age. Animals were allowed 10 days a pre-experimentation period to adapt to laboratory conditions in order to stay away from any complications along with the experiment. They were housed in metabolic cages and received water and food with fresh supplies presented daily.

Drugs:

Monosodium Glutamate (MSG) was purchased from Loba Chemie Company and was administered orally at doses of 10 mg/kg b.wt. daily for two months Onaolapo, O.J. and Onaolapo, A.Y., (2016), Kushwaha and Bharti, (2015) and Abdulsalam, H., *et al.* (2018).

Nano-curcumin was purchased from NanoTech Egypt for Photo-Electronics,

El-Wahaat Road, Dreamland city, Entrance 3, City of 6 October, Giza, Egypt.

Animals were divided into four groups each containing 10 rats.

The first group (Control group) was left as normal control. The second group (Nano-Cur group) orally received a daily dose of Nano-Cur (100 mg/kg b. w.) 3 times a week for eight weeks. The third group (MSG group) was orally administered with 10 mg/kg b. w. for 8 weeks. The fourth group (Therapeutic group) was treated with an oral dose of MSG daily for 4 weeks then administrated an oral dose of Nano-Cur for another 4 weeks.

Half of the animals were sacrificed after 4 and another one was sacrificed after 8 weeks. The samples of the blood were collected independently in glass tubes, then centrifuged for 15 minutes at 3000 rpm and stored at -20°C till biochemical analysis.

BioMed Diagnostic Co. kit was used for the determination of lipid profile, liver function, Malondialdehyde (MDA).

Statistical Analysis:

The SPSS for windows programming was utilized for factual examination, variant 10.0. Examination of change (ANOVA) which means that the scattering or contrast between multiple means to the determined standard deviation of this distinction was evaluated, Tello, R. and Crewson, P.E. (2013).

RESULTS

Lipid Profile Tests:

Serum Cholesterol, T.G, HDL and LDL level:

From the examination in the information introduced in the table (1) no amazing changes were noted in the degree of serum cholesterol, fatty oil (TG), HDL and LDL of typical control rodents and Nano-Cur rodents bunch. Then again, in MSG bunch a critical rate height was acknowledged in the degree of cholesterol, fatty oil (TG), HDL and LDL in MSG rodents' bunch for a considerable length of time was recorded when contrasted with control rodents. Additionally, a checked abatement happened in lipid profile levels in the restorative rodents' bunch that was time subordinate. (Table 1).

Table 1: The therapeutic role of Nano-Cur on cholesterol, triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (mg/dl) levels in control and experimental groups.

Parameters	Group		Control group N=10	Nano-Cur Group N=10	MSG Group N=10	Therapeutic Group N=10
	Duration	Mean±S.E				
Cholesterol(mg/dl)	30 days	Mean±S.E	60.36 ^A ±0.53	61.31 ^A ±0.20	85.51 ^B ±0.41	86.71 ^B ±0.35
		% Change		1.574%	41.667%	48.625%
	60 days	Mean ±S. E	61.32 ^A ±???	60.25 ^A ±0.41	98.23 ^B ±0.61	79.20 ^D ±0.60
		% Change		-1.745%	60.192%	29.159%
T.G (mg/dl)	30 days	Mean±S.E	52.91 ^A ±0.74	52.12 ^A ±0.61	102.50 ^B ±0.90	100.91 ^B ±0.91
		% Change		-1.493%	93.725%	90.720%
	60 days	Mean±S.E	53.01 ^A ±0.82	52.36 ^A ±0.30	123.92 ^B ±0.71	86.16 ^D ±0.50
		% Change		-1.226%	133.767%	62.535%
HDL (mg/dl)	30 days	Mea ±S.E	8.50 ^A ±0.53	8.71 ^A ±0.71	4.13 ^B ±0.23	3.91 ^C ±0.32
		% Change		2.471%	195.529%	214.353%
	60 days	Mean ±S. E	8.61 ^A ±0.35	8.21 ^A ±0.39	3.21 ^B ±0.31	7.32 ^D ±0.20
		% Change		-4.65%	-62.72 %	-14.98 %
LDL (mg/dl)	30 days	Mean±S.E	42.62 ^A ±0.32	43.51 ^A ±0.28	83.15 ^B ±0.51	85.60 ^D ±0.62
		% Change		2.088%	95.096%	100.844%
	60 days	Mean ±S. E	42.51 ^A ±0.29	41.62 ^A ±0.36	99.20 ^B ±0.38	78.50 ^D ±0.51
		% Change		-2.094%	133.357%	84.662%

- Data are expressed as mean ± slandered error (SE) n= number of rats
- A, B, C, D Means a common superscript within a row are significantly different (p<0.05)
- a.b Means a common superscript within a column are significantly different (p<0.05)

Function Tests:**Serum ALT & AST levels:**

The information recorded for the serum alanine aminotransferase and serum aspartate aminotransferase is introduced by table (2). Typical rodents showed pretty much consistent levels throughout the review. In addition, no astounding changes were accounted for in Nano-Cur rodents' bunch. An impressive time subordinate improvement was seen in remedial rodents (bunch getting oral portion MSG day by day for quite a long time then, at that point, regulated oral portion of MSG and Nano-Cur for a considerable length of time).

Table 2: The therapeutic role of Nano-Cur on serum ALT & AST levels in control and experimental groups.

Parameters	Group		Control group N=10	Nano-Cur Group N=10	MSG Group N=10	Therapeutic Group N=10
	Duration					
ALT (mg/dl)	30 days	Mean±S.E	30.10 ^A ±2.6	30.20 ^A ±1.7	67.62 ^B ±1.2	65.21 ^B ±0.42
		% Change		0.33%	124.65 %	106.67 %
	60 days	Mean±S.E	30.50 ^A ±1.9	31.50 ^A ±2.0	72.51 ^B ±0.70	50.61 ^D ±0.6
		% Change		3.279 %	137.738 %	65.934 %
AST (mg/dl)	30 days	Mean ±S.E	27.21 ^A ±2.10	27.50 ^A ±2.0	53.13 ^B ±2.3	52.30 ^B ±2.3
		% Change		1.06 %	95.14 %	92.20%
	60 days	Mean±S.E	26.91 ^A ±2.6	27.10 ^A ±2.1	73.12 ^B ±3.1	65.20 ^D ±1.3
		% Change		0.706 %	171.721 %	142.289 %

- Data are expressed as mean ± slandered error (SE) n= number of rats
- A, B, C, D Means a common superscript within a row are significantly different (p<0.05)
- a.b Means a common superscript within a column are significantly different (p<0.05).

Protein Profile:**Serum Total Protein and Albumin (g/dl) Levels:**

On identifying the serum total protein and albumin level, the information is given in table (3). The control and Nan-Cur rodents bunch planned pretty much steady figures during the review time frame. According to the control rodents, a huge decline in total protein level and in albumin level were detailed in rodents treated with MSG for 8weeks. In addition, partial recovery occurred in the therapeutic rats' group.

Table 3: The therapeutic role of Nano-Cur on serum total protein (g/dl) and albumin (g/dl) levels in control and experimental groups.

Parameters	Group		Control group N=10	Nano-Cur Group N=10	MSG Group N=10	Therapeutic Group N=10
	Duration					
Total protein (g/dl)	30 days	Mean±S.E	8.26 ^A ±1.32	8.31 ^A ±0.90	4.61 ^B ±0.72	4.31 ^B ±0.71
		% Change		0.60 %	-44.18%	-47.82%
	60 days	Mean ±S.E	8.31 ^A ±0.80	8.43 ^A ±0.11	3.10 ^B ±0.21	4.92 ^D ±0.8
		% Change		1.44 %	-62.69%	-40.794%
Albumin	30 days	Mean ±S.E	180.20 ^A ±1.82	182.65 ^A ±1.41	152.73 ^B ±0.91	154.20 ^B ±1.30
		% Change		1.35%	-15.24%	-14.42 %
	60 days	Mean ±S.E	183.70 ^A ±1.61	181.31 ^A ±1.40	147.90 ^B ±1.20	166.31 ^D ±2.70
		% Change		-1.30%	19.49%	-9.466%

- Data are expressed as mean ± slandered error (SE) n= number of rats
- A, B, C, D Means a common superscript within a row are significantly different (p<0.05)
- a.b Means a common superscript within a column are significantly different (p<0.05).

Oxidative Stress Parameters:**a- Malondialdehyde (MDA) Level:**

No changes were confirmed after treatment Nan-Cur (100 mg/kg b. w.) for 4 and 8 weeks (Table 4). In MSG group a huge rise was observed in tissue MDA level. These were later profoundly fundamentally expanded at the last stretch (8 weeks) (Table 4).

Moreover, halfway recuperation happened in the therapeutic rats' group.

Table 4: The therapeutic role of Nan-Cur on the tissue MDA levels in control and experimental groups.

Parameters	Group		Control group N=10	Nano-Cur Group N=10	MSG Group N=10	Therapeutic Group N=10
	Duration					
MDA (nM/ml)	30 days	Mean±S.E	0.32 ^A ±0.13	0.38 ^A ±0.2	0.70 ^B ±0.22	0.72 ^B ±0.51
		% Change		18.75%	118.75%	125%
	60 days	Mean±S.E	0.35 ^A ±0.14	0.36 ^A ±0.16	1.26 ^C ±0.25	0.60 ^E ±0.31
		% Change		2.857 %	260%	71.428%

- Data are expressed as mean ± slandered error (SE) n= number of rats
- A, B, C, D Means a common superscript within a row are significantly different (p<0.05)
- a.b Means a common superscript within a column are significantly different (p<0.05).

b-Total antioxidant capacity TAC level:

On detecting the tissue TAC level, the data are given in table (5).no changes were recorded in the Nan-Cur rats' group. A significant decrease in TAC level was reported in rats treated with MSG. A slight decrease took place in tissue TAC level in the therapeutic rats' group.

Table 5: The protective and therapeutic role of Nano-Cur on the tissue TAC levels in control and experimental groups.

Parameters	Group		Control group N=10	Nano-Cur Group N=10	MSG Group N=10	Therapeutic Group N=10
	Duration					
TAC (Mm/L)	30 days	Mean ±S.E	0.261 ^A ±0.41	0.259 ^A ±0.51	0.160 ^B ±0.01	0.170 ^D ±0.19
		% Change		-0.766 %	-38.697 %	-34.865 %
	60 days	Mean±S.E	0.262 ^A ±0.32	0.260 ^A ±0.21	0.192 ^B ±0.24	0.190 ^D ±0.30
		% Change		-0.763 %	-26.718 %	-27.781 %

- Data are expressed as mean ± slandered error (SE) n= number of rats
- A, B, C, D Means a common superscript within a row are significantly different (p<0.05)
- a.b Means a common superscript within a column are significantly different (p<0.05)

DISCUSSION

Monosodium glutamate is the sodium salt of glutamate acid. López-Miranda, V., *et al.* (2015) and Hazzaa,S.M., *et al.* (2020).MSG is deemed as one of the enhancer contents which add in the food industry in several amounts to promote the flavor of food. Hazzaa,S.M., *et al.* (2020) and Yan, L., *et al.* (2013). In the past few years, a lot of research has addressed the safety and toxicity of MSG and shown its negative impact on people Guyton,A. and Hall,J. (1996) and Airaodion, A.I. *et al.* (2019).

In addition, MSG administration causes toxicity in the liver due to oxidative stress which led to an increase in lipid peroxidation, decreased antioxidant enzymes and fibrosis Elshafey, M. *et al.* (2017) and Hajihassani, M.M. *et al.* (2020).

Curcumin is a hydrophobic polyphenol extracted from the rhizome of Curcuma longa has a vast ambit of pharmacological and biological vigor, inclusive decrease blood cholesterol, reduced blood sugar, antioxidant and anti-inflammatory properties. Curcumin has a neutralized effect on reactive oxygen species and has a protective function on the oxidative damage of biological membranes, DNA and protein in various diseases by getting rid of the radicals Zhang, D.W, *et al.* (2013) and Mantzorou,M., *et al.* (2018).

Curcumin is recognized as a potent antioxidant, Anti-mutagenic, anti-inflammatory, neuroprotection, hypoglycemia, antitumor, antimicrobial, tissue regeneration, antiangiogenic, anti-metastatic Nelson, K.M., *et al.* (2017) and Ibrahim,

R.M., Abd Elaal, F.El.A., and Zaki,S., (2019). The liver is a vital organ that gets rid of toxins that the body is exposed to, whether chemical or microbiological substances. When the liver undergoes morphological changes, the metabolic processes are affected, which leads to a defect in the detoxification process Bourdi,M., *et al.* (2002) and Li, J., *et al.* (2019).

In the present study, administration of MSG resulted in impairment in liver markers including an increase in lipid profile. These results agree with many studies that demonstrated that this elevation is due to motivation of free fatty acids from the adipose tissue to the bloodstream and elevated level of acetyl CoA leading to an increase in the synthesis of cholesterol or imputed to peroxidation lipids in cell membrane Abu Aita, N.A., and Mohammed, F.F., (2014) and Helal, E.G.E., *et al.* (2019).

In MSG treated group a huge expansion in the lipid profile values was recorded. Present outcomes are in concurrence with Okediran who saw hyperlipidemia with fundamentally raised degrees of serum TG and Cholesterol Okedira,B., *et al.* (2014).

Furthermore, elevations in serum levels of TG, TC and LDL were associated with an increase in the activity of 3-hydroxyl-3-methylglutaryl-Coenzyme A reductase "the rate-limiting enzyme in the biosynthesis of cholesterol" and also increase lipogenesis and reduced TC and TG metabolism in MSG rats group B. Okediran, *et al.* (2014) and Cemaluk, E.A.C. and Onyinye, N.O., (2011).

The current work on the liver uncovered that organization of MSG for 30 days and 60 days instigated a conspicuous expansion in AST and ALT and noticed a reduction in both all-out protein and albumin substance when contrasted with the control group. This could be credited to the creation of oxidative stress that damage liver cells El-Gharabawy, R. M., *et al.* (2019).

Moreover, the current result was attributed to decreased rate of polypeptide elongation, depletion of t-RNA in the liver and respiratory depression Li, J. *et al.* (2019). In the group treated with Nano-Cur no remarkable changes in lipid profile and liver function were revealed while amelioration was observed in the therapeutic rats' group in the same biomarkers. These results are in agreement with many authors Hasimun, P., *et al.* (2011).

In addition to that, the current observed that treatment with MSG led to disturbance in some hepatic biomarkers reflected by the significant elevation in ALT and AST, decrease in total protein and Albumin levels. These results matched with El-Gharabawy,R. M., *et al.* (2019), Onyema, O.O., *et al.* (2006) and Olguin,M.C., *et al.* (2018).

Insignificant changes were obtained in Nano-Cur rats' group throughout the experimental period in the level of lipid profile, liver enzymes, protein and albumin levels. Remarkable improvement was recorded in the therapeutic group in serum cholesterol, HDL, TG and LDL levels. The depletion in TG and cholesterol levels following Nano-Cur intake may be attributed to the influence of Nano-Cur itself as lipid metabolism El-Ezaby, M.M., *et al.* (2018).

Similarly, the response is dependent on dose and reduces the increase in TG level, cholesterol after exposure to toxic. It has been reported that antioxidants and flavonoids scavenge polyunsaturated fatty acids peroxy radicals and interrupt the chain reaction so they act as inhibitors of lipid peroxidation Salahshoor, M., *et al.* (2016). Nano-Cur ameliorated liver impairment as suggested by a significant restoration of liver enzymes. This may be because of the sped-up recovery of liver cells affected by different bioactive mixtures like flavonoids and esters present in Nano-Cur that assisted with forestalling layer delicacy and accordingly decline the spillage of marker chemicals into circulation Chattopadhyay, K., *et al.* (2018).

In the present investigation, a significant increase in the content of tissue MDA level was realized as compared with the control group. The increase in MDA presented in the current study might be a result of fibrosis of the liver generated by MSG Ibrahim, M.A., *et al.* (2019). In addition, the oxidative stress caused by MSG led to fibrosis and hepatic degeneration Yaqub, H., *et al.* (2008). Also, the increase in the influx of intracellular calcium as a result of increased glutamate level into mitochondria leads to produce reactive oxygen species (ROS) which cause cell damage Jaiswal, M.K., *et al.* (2009) and Szydłowska, K. and Tymianski, M., (2010).

In the current investigation, a significant depletion in the content tissue total antioxidant capacity TAC level in the MSG rats group compared with the control group. The decrease in TAC presented in the current study might reflect their reaction with reactive oxygen species generated by MSG Ahmed, M.H.M., (2016) and Sikka, S.C., (2001). Oxidative stress and the creation of free radicals appear to be liable for MSG poisonousness. Free radicals respond with polyunsaturated fats in the cell membrane creating lipid peroxides and destroying the cell membrane Ibrahim, M.A., (2019).

Moreover, ROS produced by the toxic levels of monosodium glutamate might have caused lipid peroxidation and enzymes depletion, which are indicators of tissue damage Ibrahim, M.A., *et al.* (2019) and Tawfik M.S. and Al-Badr, N., (2012), AL-Mosaibih, M.A., (2013) and Diniz Y.S., *et al.* (2004).

In the current work, no remarkable changes were reported after rats were treated with Nano-Cur in tissue MDA and TAC. The remedial impacts of Nano-Cur maybe because of the positive limit of Nanoparticles to go through the membrane and to aggregate in go through the cell membrane and to amass in hydrophobic and hydrophilic pieces of the cell membrane to safeguard cells against oxidative stress and scavenging free radicals. Nano-Cur can control the metabolism of lipid leading to decrease outputs of lipid peroxidation and scavenging the free radicals produced in rats Boarescu, P.M., *et al.*, (2019) and Surekha, R.H., *et al.* (2007).

The present work revealed improvement in MDA and TAC content of the therapeutic rats' group as compared with the control and Nano-Cur group. Taking into account the consequences of the current review, it could be inferred that Nano-Cur has the capacity to switch MSG incited liver oxidative injury just as to manage the metabolic enzymatic activities and major cell content for keeping up with the appropriate working of the cell and might be considered as a restorative specialist against MSG prompted harmful impacts.

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