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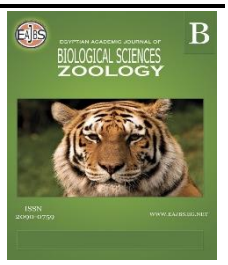

Protective and/or Therapeutic Effects of Curcumin Nanoparticles on Monosodium Glutamate Induced Cardiotoxicity in Male Albino Rats

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ABSTRACT

The flavor enhancer monosodium glutamate (MSG), which is produced from glutamic acid, is frequently used as a food enhancer in processed foods. The usage of MSG as a food additive is still debated. Moreover, curcumin, the main active compound of turmeric extract, has antioxidant, anti-mutagenic, and antimicrobial properties; additionally, it has several pharmacological activities against many chronic diseases, and its conjugation with nanomaterials increases its efficacy. This work studied the protective and therapeutic impacts of curcumin nanoparticles (CUR-NPS) on cardiotoxicity persuaded by MSG. In this work, 40 adult male albino rats were used and divided into five groups (8 rats per group): control, CUR-NPS, MSG, therapeutic, and protective groups. At the end of the treatment period, the rats were sacrificed, and then the biochemical, molecular, and histopathological investigations were performed. The outcomes demonstrated that the curcumin nanoparticles reduced the levels of malondialdehyde (MDA), lactate dehydrogenase (LDH), creatine kinase-MB (CK-MB), endothelin-1 (End-1), heart fatty acid binding proteins (HFABP), calcium (Ca^{+2}), and DNA damage while elevating the levels of both nitric oxide (NO) and total antioxidant capacity (TAC). Moreover, CUR-NPS improved the histopathological changes in heart tissue.

INTRODUCTION

Food additives are substances found naturally or synthesized and applied to the food industry in tiny amounts to enhance the taste, color, look, and quality of food (Khodjaeva *et al.,* 2013; Moldes *et al.,* 2017). They have been categorized into twenty-five classes (Martins *et al.,* 2019). Among them is monosodium glutamate (MSG). MSG is the sodium salt of a nonessential amino acid, glutamic acid. It is frequently utilized as a seasoning, stabilizing, and flavoring agent to increase the deliciousness of food products (Hajihasani *et al.,* 2020; Banerjee *et al.,* 2021a). It has been found naturally in tiny amounts in many types of food, including vegetables, meats, cheeses, and seafood (Gottardo *et al.,* 2022; AlThobaiti, 2023); currently, MSG has been added to processed food products, canned vegetables, soups, and dietary supplements (Celestino *et al.,* 2021; Xu *et al.,* 2022). It is

used frequently by Japanese and Chinese people (Acar, 2021). Despite the FDA's declaration that MSG is safe for humans (Shrestha *et al.,* 2018), the use of MSG as a food enhancer is still doubtful (Shukry *et al.,* 2020). Previous studies have demonstrated that MSG ingestion is accompanied by numerous disorders, including obesity, which is associated with hypertension and changes in cardiovascular autonomic function (Thongsepee *et al.,* 2022; Konrad *et al.,* 2012). Furthermore, various damages were found in the liver, heart, brain, and reproductive organs (Albrakati, 2023; Abd-Elkareem *et al.,* 2021; Banerjee *et al.,* 2021 a; Abdel-Aziem *et al.,* 2018). MSG intake can cause damage by elevating the production of reactive oxygen species (ROS), altering redox stability, and disrupting the equilibrium between free radicals and antioxidant levels (Banerjee *et al.,* 2020). Oxidative damage is the primary mechanism of MSG-induced cytotoxicity (Singh and Ahluwalia, 2012). In addition, MSG affects glutamate receptors, which may enhance the release of neurotransmitters involved in normal physiological activities (Abdallah *et al.,* 2014). Prior studies indicated that MSG increased MDA levels while decreasing antioxidant enzymes. In this context, Kassab *et al.* (2022) and Gad *et al.* (2021) found a marked elevation in MDA, the main product of lipid peroxidation, and a reduction in antioxidant enzymes in different organs of rats treated with MSG. Furthermore, MSG can induce DNA damage, resulting in genotoxicity (Albrahim and Binobead, 2018). Studies have recently reported that MSG can alter biomarkers of heart function. Hazzaa *et al.* (2020) and Banerjee *et al.* (2021b) found that administering MSG to albino rats increased the activities of biomarkers of heart functions, including troponin T, CK-MB, and LDH. Additionally, HFABP is abundant in striated muscle cytoplasm and released during heart dysfunction; it is one of the vital markers of cardiac injury (Okamoto *et al.,* 2000). It is associated with fatty acid metabolism because of its role in oxidation through transporting fatty acids from the cell membrane to the mitochondria. Moreover, endothelin-1 (End-1) is a vasoconstrictor peptide released by endothelial cells, fibroblasts, and myocardial cells. Many medical disorders are associated with it, including pulmonary arterial hypertension, chronic kidney disease, myocardial hypertrophy, fibrosis, oxidative stress, and apoptosis (Olivan-Viguera *et al.,* 2022; Kedzierski and Yanagisawa, 2001; Wanecek *et al.,* 2000). Antioxidants, on the other hand, are chemicals that inhibit ROS absorption **(**Ranjbar *et al.,* 2006). It has been confirmed that they have a vital role in regulating many pathological and physiological processes. They protect the organs from the damaging effects of ROS. Curcumin is one of these antioxidants **(**Otuechere *et al.,* 2014). It is an essential component of C. longa rhizomes (Heger *et al.,* 2014). Curcumin has antioxidant, anti-mutagenic, anti-tumor, anti-inflammatory, and antimicrobial effects (Nelson *et al.,* 2017; da Silva *et al.,* 2018; Willenbacher *et al.,* 2019). Moreover, it has several pharmacological effects against a variety of chronic disorders, including chronic kidney diseases (Alvarino and Yanwirasti, 2019), diabetes (Nabavi *et al.,* 2015), and cardiovascular diseases (Bhullar *et al.,* 2013). Curcumin therapy has limited efficacy. As a result, the researchers have employed nanocarriers to improve curcumin activity **(**Petrovska, 2012)**.** Nanoparticles have superior physiological and biochemical characteristics, such as light absorption, melting point, and catalytic activity, resulting in improved performance over their bulk counterparts (Paull *et al.,* 2003). Previous studies revealed that nanoparticles can enter organisms over the cell membrane and interact with biological systems. Moreover, they have many advantages, including bioavailability, delivering drugs to target organs, and overcoming traditional therapy problems (Auría-Soro *et al.,* 2019). However, no reports focused on the therapeutic and protective impacts of CUR-NPS on cardiotoxicity associated with MSG treatment in rats. So, this study aimed to investigate which is more effective in reducing cardiotoxicity induced by MSG: the administration of CUR-NPS before or after MSG treatment.

MATERIALS AND METHODS

Chemicals:

MSG was brought from LOBA Chemie Pvt. Ltd. Co., Mumbai, India; catalog number 6106-04-3; its molecular weight is 187.13 g/mol; purity is 99%. CUR-NPS was brought from NanoTech Egypt for Photo-Electronics, Giza, Egypt.

Characterization of CUR-NPS:

1.Transmission Electron Microscope:

By using transmission electron microscopy (JEOL, JEM-2100 PLUS) at room temperature and an accelerating voltage of 200 kV, the morphology and average size of CUR-NPS were ascertained. In order to ascertain the form and surface of CUR-NPS, the photos were captured at an adequate magnification.

2. Zeta Potential:

Using the Malvern zeta sizer MAL1071664, dynamic light scattering was used to determine the zeta potential of CUR-NPS.

Animals:

In this study, forty male albino rats (160–180 g) were used. The animals were given ten days to adjust to the laboratory environment. They were kept in stainless steel cages and received food and water daily at a constant temperature of 24±2 °C with a 12-hour light/dark cycle. Experimental procedures were performed according to the institutional animal care instructions of the Faculty of Women for Arts, Science and Education, Ain Shams University (sci1332306004).

Experimental Design:

Following the adaptation period, the animals were divided into five groups (8 rats per group). The control group received 2 ml of saline for eight weeks. CUR-NPS group; the rats were firstly treated with 2 ml of saline for four weeks, followed by CUR-NPS at a dose of 100 mg/kg/day, according to Boarescu et al.(2019), dissolved in distilled water, according to Du Preez et al. (2019) for another four weeks, MSG group in which the animal treated with 2 ml of saline for the first four weeks followed by 10 mg/kg/day of MSG according to Egbuonu et al. (2010**)** for another four weeks, therapeutic group; the rats treated with MSG (10 mg/kg/day) for four weeks then administered CUR-NPS (100 mg/kg/day) for the next four weeks, and protective groups; the rats were supplemented with 100 mg/kg/day of CUR-NPS for the first four weeks and followed by 10 mg/kg from MSG for the next four weeks. At the end of the treatment period, the rats from different groups were sacrificed by fast decapitation. All animals were treated once a day with a gastric tube.

Samples Collection:

After the animals' scarification, blood samples were collected and centrifuged for 15 minutes at 3000 rpm. In addition, the hearts of animals from different groups were dissected and divided into two parts. In the first part, six hearts from each group were weighed and homogenized in 1M/L phosphate buffered saline (PH 7) and centrifuged at 3000 rpm for 15 minutes. Both serum and supernatant were kept at -20 °C until the performance of the biochemical investigation. In the second part, two hearts from each group were fixed in a 10% formalin solution for histological examination. During dissection, a piece of the left ventricle of the hearts of animals from various groups was cut and stored in 10% DMSO for the comet assay.

Biochemical Analysis:

Estimation of Cardiac Oxidative Stress:

It was estimated using colorimetric methods for MDA and TAC (Bio-Diagnostic, Egypt) as previously demonstrated by Ohkawa *et al.* (1979) and Koracevic *et al.* (2001), respectively.

Determination of Nitric Oxide (NO) and Calcium Concentration:

The colorimetric determination of serum NO (Bio-Diagnostic, Egypt) was carried out according to Montgomery and Dymock (1961). Cardiac calcium concentration (Bio-Diagnostic, Egypt) was evaluated according to the method of Ginder and King (1972).

Estimation of Cardiac Markers:

Serum CK-MB (Diamond Diagnostics, Egypt) was determined according to the method of Wu *et al. (*2007). The activity of LDH (BioMed-Diagnostics, Egypt) was assessed in cardiac tissue according to the previous methods described by Belfield and Goldberg (1971).

ELISA Technique:

Determination of Serum End-1: Serum Endothelin-1 levels were determined using a kit obtained from Immuno-Biological Laboratories Co., Ltd., USA, catalog number 27167. The kit used two different types of highly specific antibodies in a solid-phase sandwich ELISA. Tetramethylbenzidine was served as a chromogen. The amount of Rat Big End-1 in the coloration corresponds to its strength.

Determination of Cardiac HFABP: Cardiac HFABP levels were measured using a kit bought from Kamiya Biomedical Company, USA, catalog number KT-479. The assay utilized a peroxidase from horseradish-conjugated anti-rat HFABP antibody for detection and an affinity-purified anti-rat HFABP antibody for solid-phase immobility (microtiter wells). In the microtiter wells, the testing samples were diluted and incubated with the conjugate for 60 minutes. Rat HFABP molecules were thereby sandwiched between the immobilization and antibody detection processes. After that, the wells were cleaned to dispose of the free HRP-labeled antibodies. Then, the tetramethylbenzidine (chromogen reagent) was added and left at room temperature for 20 minutes until the color formed. The stop solution was then added, and the yellow color was developed and measured by a spectrophotometer at 450 nm.

The Comet Assay: According to Singh *et al.* (1988), single-cell gel electrophoresis, often known as the comet assay, is used for the detection of DNA breakage in a single cell. In this method, just a few cells from the heart were inserted into a thin layer of agarose. Electrophoresis, lysis, and labeling with fluorescent DNA intercalating dye (Ethidium bromide) were the next steps. Damaged DNA fragments travel more quickly than unharmed DNA. There was the formation of a comet-like shape with a head made of intact DNA and a tail made of broken DNA. The ideal lysis is alkaline, as it distinguishes between alkali-labile sites, double-strand breaks, and single-strand breaks.

Histopathological Studies:

The histological examination of cardiac tissue was assessed according to Bancroft and Stevens (1996). The cardiac tissue was fixed in 10% formalin, then dehydrated with an ethanol series starting at 70% and ending with an absolute, paraffin-embedded section. After staining with H &E, the sections were examined using an electric microscope.

Statistics:

The data was statistically analyzed with SPSS software (version 23) and presented as the mean± standard error of the mean (SEM). For multiple comparisons, one-way ANOVA and the LSD post hoc test were used in the statistical analysis. A significance level of $P<0.05$ was assumed.

RESULTS

Characterization of the CUR-NPS:

Transmission electron microscope imaging and analysis of CUR-NPs showed that the particles were irregular in shape and their average size was 73.26 nm in diameter (Fig.

1 A & B). Moreover, the results of the zeta potential of CUR-NPS (-25.4 mv) indicated the high stability of the prepared CUR-NPS (Fig. 1C).

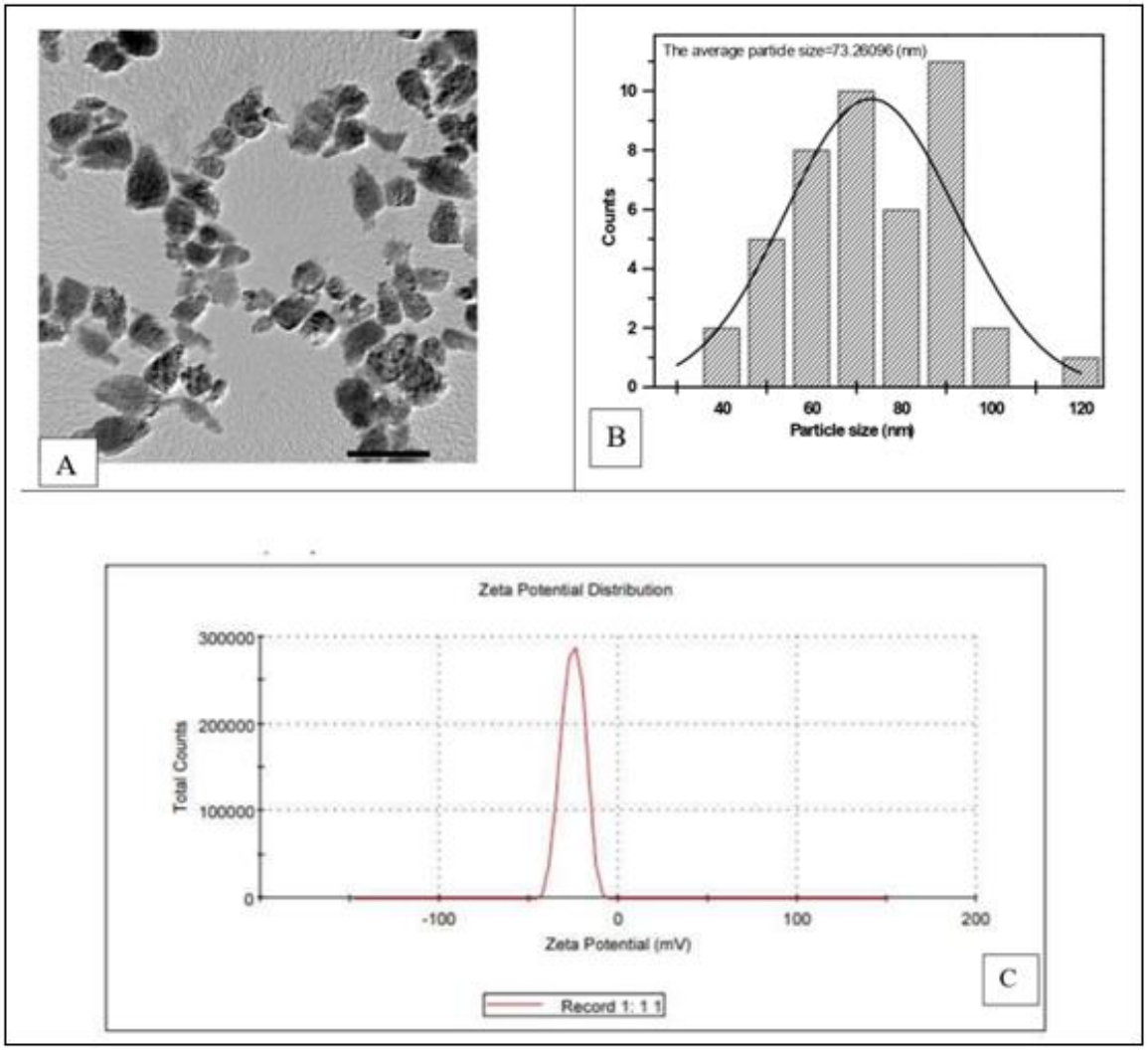

Fig.1. Characterization of CUR-NPS; (A): TEM micrograph; (B): Histogram of the average particles size; (C): Zeta potential histogram.

The Impact of CUR-NPS on MSG-induced Oxidative Stress:

The data displayed a significant elevation in MDA levels in rats treated with MSG (197.30%) related to the control group. Furthermore, partial improvement took place in the protected rats group. The percentage of their decline reached 35.14% in MDA levels at the end of the experiment. Moreover, a minor decrease in cardiac MDA levels took place in the therapeutic rats' group (124.32%) (Table 1).

Contrary to this, compared to control rats, animals given MSG had lower levels of TAC (-51.57%). Moreover, the protected rats' group revealed an elevation in TAC by the end of the experiment (-28.11%), furthermore, the therapeutic rats' group showed a minor improvement in TAC level (-39.50%) when compared with MSG-treated animals (Table 1).

The Impact of MSG and CUR-NPS on NO:

The serum level of NO was significantly decreased (-31.04%) in MSG-treated rats when compared to control rats. However, the rats in both the protective and therapeutic groups showed elevated levels of NO (-12.99% and -24.57%, respectively) when compared with MSG-exposed rats. The protective group showed the greatest improvement (Table 1).

Curative Role of CUR-NPS on Elevated Level of Calcium:

When compared to control rats, daily consumption of MSG dramatically elevated calcium levels (279.59%). Furthermore, CUR-NPS therapy reduced elevated calcium levels in both therapeutic and protective groups compared to rats treated with MSG alone (141.49% and 93.87%, respectively). The protective group showed the greatest improvement (Table 1).

Table 1: Table 1: The effect of monosodium glutamate (MSG) and curcumin nanoparticles (CUR-NPS) administration on malondialdehyde (MDA), total antioxidant capacity (TAC), nitric oxide (NO), and Calcium levels in different groups.

	Control	CUR-NPS	MSG	Protective group	Therapeutic group
MDA (µmol/g tissue)	0.37±0.02	0.36±0.02	1.10±0.06 [ab]	0.50±0.02 [abc]	0.83±0.02 [abcd]
% of change		-2.70	197.30%	35.14%	124.32 %
TAC (mmol/ g tissue)	37.17±0.95	38.83±1.19	18.00±0.71 [ab]	26.72±0.83 [abc]	22.49±0.79 [abcd]
% of change		4.47%	-51.57 %	-28.11%	-39.50%
NO (µmol/ml)	69.59±2.99	67.77±1.16	47.99±1.44 [ab]	60.55±2.58 [abc]	52.49±2.15 [abcd]
% of change		-2.62%	-31.04%	-12.99%	-24.57%
Calcium (mg/g tissue)	1.47±0.09	1.56±0.04	5.58±0.28 [ab]	2.85±0.11 [abc]	3.55±0.25 [abcd]
% of change		6.12%	`279.59%	93.87%	141.49%

Values expressed as mean ± SEM of 6 rats/ group. [a] = significant change from control group, [b] = significant change from CUR-NPS group, [c] = significant change from MSG treated group, and [d] = significant change from protective group. The mean difference is significant at the 0.05 level (P<0.05).

CUR-NPS Alleviates MSG-Induced Cardiac Dysfunction:

The present data revealed a significant increase in CK-MB, LDH, End-1, and HFABP levels in MSG-treated rats (123.06%, 113.57%, 259.52%, and 234.77%, respectively) compared with control rats. Moreover, a considerable improvement was noticed in the protected group (39.46%, 47.96%, 50%, and 67.41% for CK-MB, LDH, End-1, and HFABP, respectively): while a minor improvement occurred in cardiac parameters in the therapeutic group (96.60%, 76.02%, 161.91%, and 132.98% for CK-MB, LDH, End-1, and HFABP, respectively) compared to the MSG-treated rats (Table 2).

Table 2: The effect of MSG and CUR-NPS administration on creatine kinase-MB (CK-MB), lactate dehydrogenase (LDH), endotheilin-1 (End-1), and heart fatty acid binding protein (HFABP) levels in different groups.

	Control	CUR-NPS	MSG	Protective group	Therapeutic group
CK–MB (U/ml)	2.94±0.16	3.59±0.12	6.58±0.41 [ab]	4.10±0.17 [ac]	5.78±0.28 [abcd]
% of change		22.1%	123.06%	39.46%	96.60%
LDH (U/g tissue)	2.21±0.30	2.24±0.32	4.72±0.44 [ab]	3.27±0.38 [abc]	3.89±0.33 [abcd]
% of change		1.36%	113.57%	47.96%	76.02%
End-1 (pg/ml)	0.42±0.014	0.44±0.011	1.51±0.017 [ab]	0.63±0.017 [abc]	1.10±0.025 [abcd]
% of change		4.76%	259.52%	50%	161.91%
HFABP (ng/g tissue)	15.13±0.60	15.53±0.64	50.65±1.28 [ab]	25.33±0.78 [abc]	35.25±0.68 [abcd]
% of change		2.64%	234.77%	67.41%	132.98%

Values expressed as mean ± SEM 6 rats/ group. [a] = significant change from control group, [b] = significant change from CUR-NPS group, [c] = significant change from MSG treated group, and [d] significant change from protective group. The mean difference is significant at the 0.05 level (P<0.05).

Comet Assay Analysis:

MSG treatment elevated comet assay parameters, including comet percentage, tail DNA percentage, tail length, tail moment (TM), and olive tail moment (70.91%, 129.84%, 86.54%, 332%, and 186.36%, respectively), while it decreased the percentage of head DNA by -5.97% compared to control rats. Moreover, the protected rats' group demonstrated significantly lower DNA damage parameters by 20%, 20.27%, 25.35%, 136%, and 74.24% for comet percentage, tail DNA percentage, tail length, tail moment, and olive tail moment, respectively. On the other hand, it showed an increase in head DNA percentage (-0.86%) compared to MSG-treated rats. Furthermore, the therapeutic group also showed a slight improvement in comet assay parameters (43.03%, 88.83%, 53.36%, 224%, and 109.09% for comet percentage, ail DNA percentage, tail length, TM, and olive tail moment, respectively) when compared to the MSG group. It also showed a slight rise in head DNA percentage (-4.09%) compared to MSG-treated rats (Table 3).

Table 3: The effect of MSG and CUR-NPS administration on comet assay parameters in different groups.

	Control	**CUR-NPS**	**MSG**	**Protective group**	**Therapeutic group**
Comet percentage	8.25±0.17	7.97±0.24	14.10±0.61 ^{ab}	9.90±0.56 ^{abc}	11.80±0.67 ^{abcd}
% of change		-3.39%	70.91%	20%	43.03%
Head DNA percentage	95.61±0.63	96.07±0.50	89.90±0.64 ^{ab}	94.79±0.43 ^{c}	91.70±0.59 ^{abcd}
% of change		0.48.11%	-5.97%	-0.86%	-4.09%
Tail DNA percentage	4.39±0.66	3.93±0.53	10.09±0.64 ^{ab}	5.28±0.43^{c}	8.29±0.59^{abcd}
% of change		-10.47%	129.84%	20.27%	88.83%
Tail length	6.39±0.35	6.43±0.36	11.92±0.75 ^{ab}	8.01±0.48 ^{abc}	9.80±0.52 ^{abcd}
% of change		0.63%	86.54%	25.35%	53.36%
Tail moment (TM)	0.25±0.02	0.33±0.02	1.08±0.14 ^{ab}	0.59±0.08 ^{abc}	0.81±0.04 ^{abcd}
% of change		32%	332%	136%	224%
Olive tail moment	0.66±0.03	0.64±0.04	1.89±0.3 ^{ab}	1.15±0.10 ^{abc}	1.38±0.07 ^{abc}
% of change		-3.03%	186.36%	74.24%	109.09%

Values expressed as mean ± SEM 6 rats/ groups. ^{a} = significant change from control group, ^{b} = significant change from CUR-NPS group, ^{c} = significant change from MSG treated group, and ^{d} = significant change from protective group. The mean difference is significant at the 0.05 level ($P<0.05$).

The alkaline comet assay, which was used to detect single-strand breaks in the hearts of rats from various groups, revealed that rats in the control group did not exhibit any comets, whereas MSG glutamate exposure increased DNA strand breakage, which in turn increased DNA migration from the nucleus into the comet in the heart tissue cells. Furthermore, animals in both the protective and therapeutic groups exhibited significant improvement in comets with shorter tails (Fig. 2).

The Effect of CUR-NPS on Histopathological Changes in Heart Tissue:

Heart sections stained with H and E were observed for pathological variations in the control and treated groups. The heart section of the control group revealed normal cytoarchitecture (Fig. 3). Moreover, the cardiac sections of MSG-treated rats showed several pathological changes, including myocardium necrosis, pyknotic nuclei, hemorrhage of dilated blood capillaries between muscle fibers, and inflammatory cell infiltration (Fig. 3). Furthermore, an improvement was seen in the heart tissue of animals treated with CUR-NPS and MSG (Fig. 3). The therapeutic group showed less improvement than the protected group.

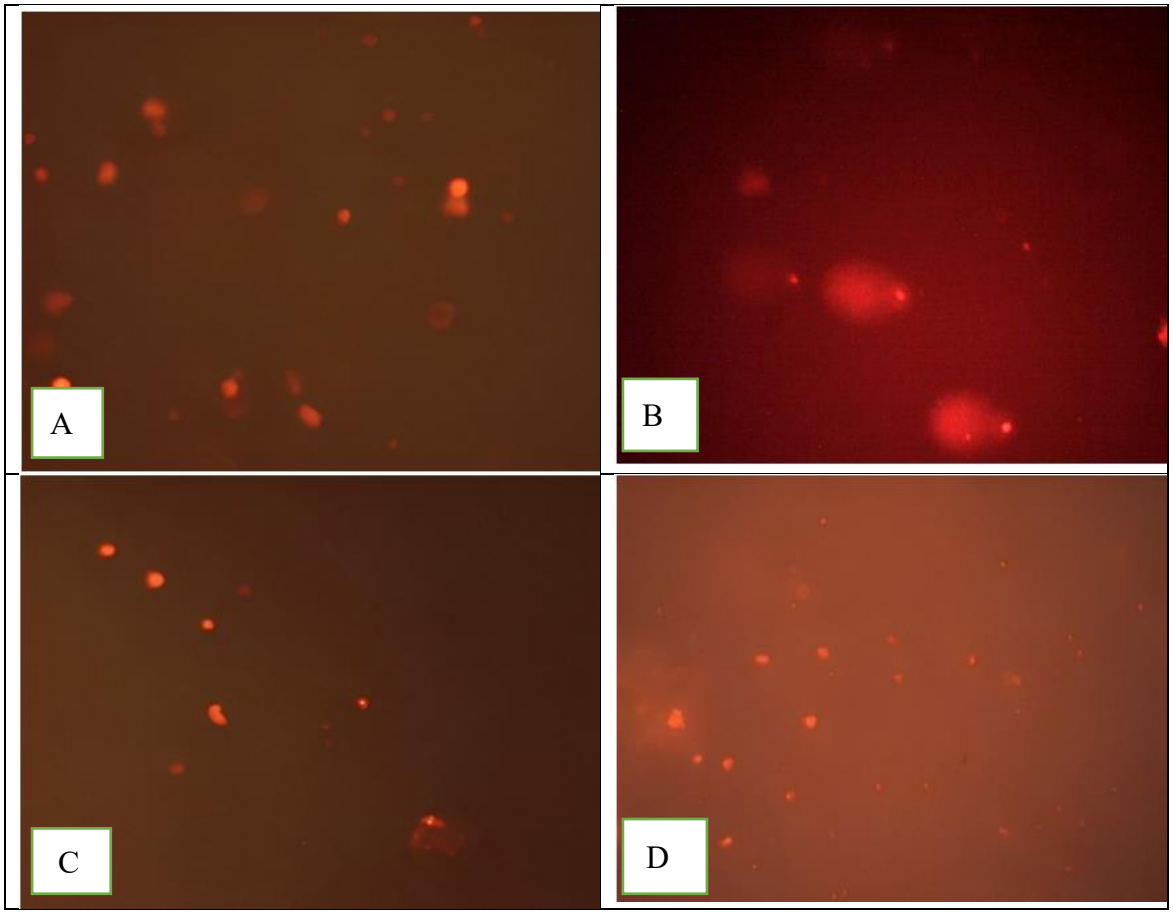

Fig. 2. Comet assay showing DNA damage; (A): control rats showed intact heads and no tails; (B): MSG rats showed an increase in comet tail length; (C and D): protective and therapeutic groups showed an improvement in comet tail lengths.

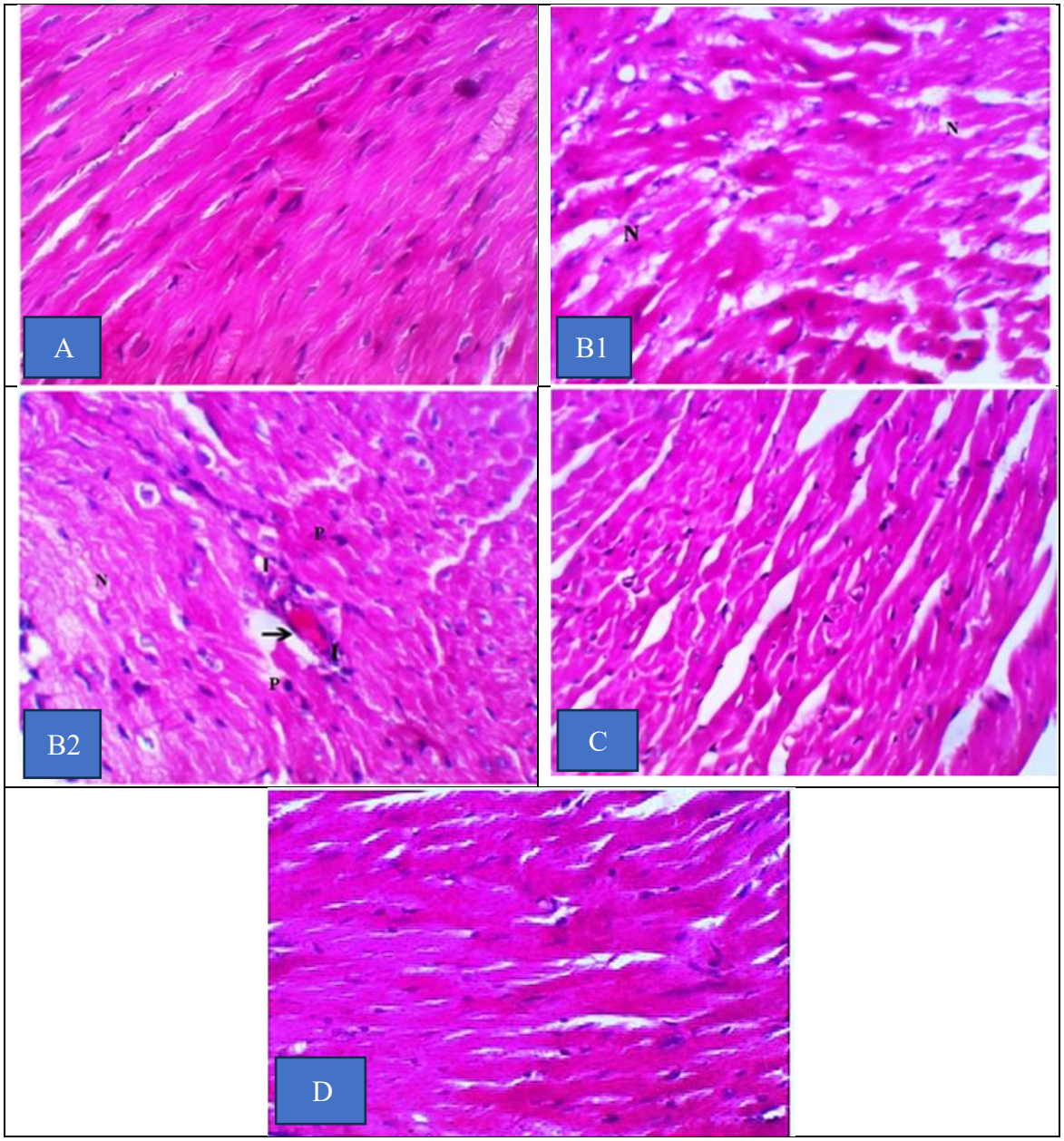

Fig. 3: Histopathological report for the heart of rats of different groups : (A) depicted the control group, with normal cyto-architecture of the myocardium; (B1 and B2) depicted the MSG group, with necrotic changes in muscle fibers (N) as well as congestion of blood vessels (arrow); inflammatory cells (I) and pyknotic cells (P); (C) depicted the protective group, with an improvement and less loss of myofibrils; (D) depicted the therapeutic group, with moderate loss of myofibrils. H & E stain, Magnification ×400

DISCUSSION

MSG is extensively utilized as a food additive and taste enhancer in various amounts; nonetheless, monosodium glutamate ingestion causes oxidative stress to various parts of the body, and its potential benefits and negative consequences on humans are unclear (Hazzaa *et al.,* 2020). MSG treatment can promote a change in metabolism, which may play a role in the progression of acute body disturbances (Ibrahim *et al.,* 2019 a). Moreover, curcumin is a powerful antioxidant, anti-inflammatory, anti-microbial, and anti-metastatic (Nelson *et al.,* 2017; Ibrahim *et al.,* 2019 b). When curcumin conjugates with

nanoparticles, the availability of curcumin increases, thereby increasing its efficacy in clinical applications (Sultana *et al.,* 2011; Ibrahim *et al.,* 2019 b).

In this study, the cardiac levels of MDA were significantly elevated in MSG-treated rats, but the levels of TAC were significantly reduced. Similarly, the prior work of Gad *et al.* (2021) and Hazzaa *et al.* (2020) found an increase in MDA and a reduction in total antioxidant enzymes. These changes contributed to the excessive production of ROS, which diminishes antioxidants and increases lipid peroxidation (Karaboduk *et al.,* 2015). Moreover, Paul and his colleagues linked the increase in lipid peroxidation indicators in the heart muscle of MSG-treated rats to the oxidative stress caused by glutamate toxicity, which is linked to glutamate receptor over-excitation (Paul et al., 2012). After entering the body, MSG is absorbed and transformed into Na^+ and L-glutamate. The central nervous system, as well as many other organs, including the heart, have glutamate receptors (Gill and Pulido, 2001). According to Mirzakhani *et al.* (2020), glutamate or glutamate analogs can excite glutamate receptors (mostly those found in the heart). In turn, this resulted in the overproduction of ROS and increasing lipid peroxidation because of the increased intracellular mobilization of calcium. Hence, these fluctuations may lead to organ malfunction and enzymatic disorders. Furthermore, MSG can alter lipid intensity as well as lipoprotein fractions, which cause obesity and, in turn, the induction of lipid peroxidation and oxidative damage (Amirkhizi et al*.,* 2010; Banerjee *et al.,* 2021 b).

In this study, rats given MSG showed a decrease in NO levels. These findings are in line with the prior findings of Abd-Elkareem *et al.* (2021), who discovered a reduction in NO levels in MSG-treated rats' serum. The decreased NO level in the serum of the MSG group suggests a decrease in cellular resistance to oxidative and nitrosative damage (Abd-Elkareem *et al.,* 2021). Furthermore, Lobato *et al.* (2011) related the reduction in NO to a reduction in endothelial nitric oxide expression. Furthermore, as previously indicated, the decrease in NO levels might be attributed to higher End-1 levels (Genovesi *et al.,* 2022). On the other hand, CUR-NPS supplementation improved the levels of MDA, NO, and TAC. These findings are consistent with the findings of Sarawi *et al.* (2021a, 2021b), who observed that CUR-NPS improved cardiac MDA and antioxidant enzymes in copper sulfate-intoxicated rats. Furthermore, many studies indicated that CUR-NPS significantly improved the oxidative stress caused by several toxic agents in both in vivo and in vitro models (El-Desoky *et al.,* 2020; Zaki *et al.,* 2020). CUR-NPS's antioxidant activity is attributed to its capability to counteract free radicals (Mohammed et al., 2018) as well as its ability to enhance glutathione production (Biswas *et al.,* 2005). This could provide an explanation for the capability of CUR-NPS to inhibit free radical generation and improve lipid peroxidation. Furthermore, Yadav *et al.* (2012) said that CUR-NPS reduced the levels of thiobarbituric acid reactive substances, and therefore, the antioxidant status improved due to the nanoparticle's prolonged circulation duration in the blood, which increased its bioavailability and effectiveness. Another explanation is that several nanoparticles' structures can activate the Nrf2/HO-1 signaling pathway, which can modulate antioxidant status and reduce the risk of oxidative damage (Mahmoud *et al.,* 2019; Cui *et al.,* 2021; Mo *et al.,* 2022). So, CUR-NPS may reduce oxidative damage through the same mechanism. In this work, the calcium level was increased by MSG treatment. This result follows a previous study by Choudhary *et al*. (1996). This elevation could be due to amplified oxidative stress (Choudhary *et al.,* 1996). Also, the high calcium level may be due to the elevated levels of glutamate (Winter and Baker, 1995), which result from the degradation of MSG. The elevated levels of glutamate can stimulate NMDA receptors in cardiac tissue. As a result, the calcium concentration rises. Moreover, CUR-NPS treatment attenuated the elevated level of calcium. This improvement may be attributed to the capability of curcumin nanoparticles to reduce the levels of glutamate (Noor *et al.,* 2022); as a result, the levels of calcium are reduced. Furthermore, according to Mohammed *et al.* (2020), the inhibition of

Na-K ATPase may elevate the cytoplasmic levels of Ca^{+2} in cardiac cells. CUR-NPs can increase the activity of Na-K ATPase, which may help restore the ionic gradients, including calcium, on both sides of the cardiac cell to their normal level (Mohammed et al., 2020). Also, the reduction of ROS production by CUR-NPS may be the main reason for the calcium reduction.

The data from the current work found a considerable increase in LDH and CK-MB activities in rats treated with MSG. These findings are consistent with those of Banerjee *et al.* (2021a), Hassan *et al.* (2020), and Hazzaa *et al.* (2020). Together, they reported an increase in cardiac enzyme activity after MSG treatment. Taniyama and Griendling (2003) proved that ROS has a vital role in cardiotoxicity. Hence, MSG administration can induce oxidative damage which may result in myocardial dysfunction. Likewise, the toxicity of MSG can lead to the destruction of the myocardial cells and, following this, a lack of oxygen or glucose. Then, the membrane of cardiac cells becomes permeable, and a large number of enzymes including CK-MB are released into the bloodstream and their concentrations increase in the serum (Baky *et al.,* 2009; Ganesan *et al.,* 2013).

Few studies in animal models demonstrated the effect of toxic agents on HFABP. In this study, MSG treatment elevated cardiac HFABP. Similarly, Hasić *et al.* (2011) discovered an increase in HFABP in male albino rats following isoproterenol administration. Elnoury *et al.* (2022) also reported that doxorubicin administration elevated the serum level of HFABP in rats. In addition, many authors indicated an increase in HFABP in patients with different diseases, including cancer (Yuan *et al.,* 2021), pulmonary disease (Sato *et al.,* 2018), and cardiotoxicity induced by carbon monoxide (Elhelaly *et al.,* 2020). This increase might be attributed to the protein's continual release from cardiac muscle cells (Pritt *et al.,* 2008). Furthermore, Hasić *et al.* (2011) said that the rise in HFABP might be due to cardiac cell injury, which could be caused by Ca^{2+} overload caused by catecholamine action; MSG may raise the amount of HFABP by a similar mechanism.

Fatty acid-binding proteins are cellular lipid transporters and are involved in the intracellular control of lipid transport. According to Rodríguez-Calvo *et al.* (2017, 2023), HFABP is a member of the fatty acid-binding proteins group linked to metabolic illnesses like diabetes and obesity that cause heart diseases. Furthermore, prior studies have shown that MSG is linked to obesity through several pathways, including an increase in triglyceride and cholesterol levels (Kazmi *et al.,* 2017). These findings were found in the previous work on MSG (Mohamed *et al.,* 2022). Consequently, MSG can dysregulate HFBP by this mechanism.

End-1 is a 21-amino acid peptide generated by endothelial cells, fibroblasts, and myocardial cells with a potent vasoconstrictor action (Olivan-Viguera *et al.,* 2022). Toxic substances can interfere with End-1 release. In the present work, MSG significantly increases the levels of End-1. Similarly, Abd El-Motelp (2022) proved that doxorubicin treatment elevated cardiac End-1 levels in male rats. Several studies have also reported an increase in End-1 levels in a variety of clinical conditions (Sandira *et al.,* 2022; Zhang *et al.,* 2021; Hernández *et al.,* 2018). The toxic agents produce ROS, which promotes endothelium dysfunction and enhances the release of End-1 (Luu *et al.,* 2018). Furthermore, the rise in End-1 levels might be due to the suppression of NO production (Ahlborg and Lundberg, 1997). Additionally, the levels of End-1 are affected by the high levels of calcium (Pache *et al.,* 2002). This study revealed that MSG could elevate the calcium levels, and as a result, it could enhance the End-1 level. Moreover, the increased levels of End-1 may be attributed to the increase in this protein expression by MSG treatment (Kawamura *et al.,* 2007).

Contrary, CUR-NPS administration improved the cardiac biomarkers that were changed by MSG exposure. It has been shown that CUR-NPS is effective in treating the hazards of toxic agents-induced cardiotoxicity. According to Alotaibi *et al.* (2021) and

Mohammed *et al.* (2020), CUR-NPS alleviated the cardiotoxicity induced by several agents in animal models. The impacts of CUR-NPS may be ascribed to its ability to neutralize free radicals and antioxidant properties, which may protect the cardiac cells from injury induced by the severe oxidative damage caused by MSG, hence inhibiting the production of cardiac markers such as LDH and CK-MB (Khadrawy *et al.,* 2021). Moreover, the studies by Alotaibi *et al.* (2021) and Swamy *et al. (*2012) indicated that both curcumin and CUR-NPS treatment reduced the release of CK-MB in female mice with Ehrlich ascites carcinoma and female rats with myocardial infarction by protecting the cardiac cells from the possibility of membrane rupture, which can lessen myocardial membrane damage and potentially reduce the amount of enzyme that leaks into the bloodstream. The CUR-NPS has a better cardioprotective impact than curcumin due to the bioavailability of curcumin nanoparticles, which improves the transport of curcumin to myocardial cells (Nabofa *et al.,* 2018).

The data collected from this study indicated that CUR-NPS provided defense against elevated End-1 levels. This finding was explained by Nehra *et al.* (2016), who showed that CUR-NPS supplementation decreased End-1 expression levels in rats with right ventricular hypertrophy, which may lead to a decrease in End-1 levels. Also, the reduction in End-1 in this work may be due to the enhancement of NO production by CUR-NPS. Additionally, CUR-NPS treatment reduced the amounts of HFABP that generated by MSG. This effect might be due to the reduction of oxidative stress, which lowered calcium levels and finally decreased HFABP. Furthermore, the protective effect of CUR-NPS is associated with its capacity to modulate the expression of several enzymatic and nonenzymatic proteins. Therefore, it can reduce HFABP levels by regulating its expression.

In the current study, MSG treatment increased comet percentage, tail length, TM, percentage of tail DNA, and olive tail moment while decreasing head DNA (%). These results coincided with those of Kandeel *et al.* (2019), who noticed a substantial increase in comet percentage, tail DNA percentage, and TM in the testes cells of mice exposed to MSG. Also, the comet assay results of the work carried out by El-Alfy *et al.* (2022) revealed a significant elevation in DNA damage (tail length, olive tail moment, and tail DNA percentage) in the liver cells of mice treated with MSG. Previous reports have shown that MSG can cause DNA damage by accumulating ROS and creating an imbalance between lipid peroxidation and the oxidative state (Sharma, 2015; Albrahim and Binobead, 2018). MDA, the major outcome of lipid peroxidation, can generate DNA adducts by reacting with the nitrogenous bases and sugar units in DNA. As a result, it might be a mutagen or carcinogen (Marnett, 1999).

On the contrary, CUR-NPS supplementation in MSG-treated rats resulted in an improvement in DNA fragmentation. In the same concern, Abdelmoneam et al. (2023) proved that CUR-NPS decline DNA damage parameters (tail length, percentage of tail DNA, and olive tail moment) in tumor tissues of Ehrlich's ascites carcinoma-bearing mice. Also, Abd-Allah and Abd El-Rahman (2022) observed that curcumin-vitamin E nanocomposite dramatically reduced DNA damage in tests of cadmium chloride–intoxicated rats, as revealed by reducing tail length, TM, percentage of tail DNA, and olive tail moment. CUR-NPS's activity is attributed to its antioxidant efficacy and ability to neutralize ROS responsible for cellular components and DNA damage (El-Desoky *et al.,* 2020). Additionally, CUR-NPS has a high capacity for penetrating the mitochondrial membrane and the nucleus, which helps to reduce oxidative damage (Abdelmoneam *et al.,* 2023). Also, according to Roy *et al.* (2011), curcumin enhanced DNA repair capacity and reduced the synthesis of 8-hydroxy-20-deoxyguanosine in the West Bengal population exposed to arsenic. However, the ameliorative effect of CUR-NPS is better than the effect of free curcumin because nanoparticles have higher bioavailability and uptake of curcumin into the cells (Sankar *et al.,* 2014).

In the present work, the heart section of the control group stained with H&E revealed a regular architecture pattern of the myocardium. Heart sections from MSG-treated rats showed degeneration of myocardial tissue, pycknotic nuclei, inflammatory cell infiltration, and congested blood capillaries. These results agreed with those of Hazzaa *et al.* (2020), Hassan *et al.* (2020), and Abo El Wafa *et al.* (2021). The abnormalities might be attributed to MSG-induced oxidative damage (Hamad, 2022), as demonstrated in the present work by a rise in MDA and a reduction in TAC. The oxidative stress triggers the nuclear factor-κB signaling pathway, which can control numerous genes linked to inflammatory responses, including tumor necrosis factor-α and the caspases family, which causes cell death (Hamad, 2022). In addition, CUR-NPS administration alleviated the pathological changes caused by MSG, which is comparable with the findings of Sarawi *et al.* (2021 a), who found that CUR-NPS reduced the histopathological abnormalities created in the hearts of copper sulfate-intoxicated rats. The modulatory impacts of CUR-NPS on cardiac tissue might be due to its ability to eliminate ROS as well as its antioxidant and anti-inflammatory properties. It has been reported that curcumin can diminish apoptosis and, consequently, cardiomyocyte injury by modulating the proinflammatory response through the downregulation of NF-κB and Bcl-2 (Lv *et al.,* 2016; Rahnavard *et al.,* 2019). Also, it can modify the rate of immune cell infiltration and enhance the mitochondrial activity of the injured cardiomyocytes (Boarescu *et al.,* 2019). Because CUR-NPS have better absorption and bioavailability than its bulk, they appear to be more biologically beneficial (Nabofa *et al.,* 2018).

Conclusion

This study concluded that MSG administration caused cardiotoxicity by inducing oxidative stress, elevating cardiac markers, altering cardiac muscle architecture, and increasing DNA damage. On the other hand, curcumin nanoparticles in protective and therapeutic doses ameliorated the cardiotoxicity induced by MSG by adjusting the changes caused by MSG. The greatest improvement was seen in the curcumin nanoparticles protective group.

Abbreviations

Ca^{+2}: Calcium
CK-MB: Creatine kinase-MB
CUR-NPS: Curcumin nanoparticles
End-1: Endothelin-1
HFABP: Heart fatty acid binding proteins
LDH: Lactate dehydrogenase
MDA: Malondialdehyde
MSG: Monosodium glutamate
NO: Nitric oxide
ROS: Reactive oxygen species
SEM: Standard error of the mean
TAC: Total antioxidant capacity
TM: Tail moment

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