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Experimental Biochemical and Histopathological Study on Monosodium Glutamate Induced Cardiotoxicity and its Alleviation by Quercetin

Rabab Shaban EL-Shafey, M.D.[1], Asmaa Y. A. Hussein, M.D. [1]*
[1]*Department of Forensic Medicine & Clinical Toxicology, Faculty of Medicine, Banha University, Egypt*

Abstract: *Monosodium glutamate (MSG) is one of food enhancer that is commonly used worldwide, and fewer studies were done about its cardiovascular effects which is common cause of morbidity and mortality in human. This study was designed to assess the cardiotoxicity of MSG and to evaluate the potential modulatory antioxidant effect of quercetin which is a natural polyphenolic flavonoid. fifty adult albino rats were divided into five equal groups: negative control; positive control; quercetin treated; MSG-treated and "MSG + quercetin" treated. A single daily dose of quercetin (50mg/kg) and MSG (4g/kg) were given orally for 45 days according to the study regimen. The present study illustrated cardiotoxic effects of MSG evidenced by a significant increase in the serum creatine phosphokinase (CK-MB) activity, cardiac troponin I (cTnI) level and tissue malondialdehyde level (MDA) along with significant decrease in tissue glutathione-s- transferase (GST) level; and histological changes in cardiac architecture (cloudy swelling with fiber separation and vascular congestion. & hemorrhage) in MSG treated group. The addition of quercetin with MSG showed significant improvement of previously mentioned changes.*

Keywords: *cardiotoxicity, flavonoids, Food enhancers, Monosodium glutamate, Quercetin.*

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I. Introduction

Monosodium glutamate (MSG) is the sodium salt of a naturally occurring non-essential amino acid (glutamic acid). It is presenting in a form of white crystalline powder [1] and consisting of 22% of sodium and water; 78% of glutamic acid which is one of the most produced amino acids in the body and plays an essential role in human metabolism [2].

Monosodium glutamate (MSG) is considered as a one of the best identified flavor enhancer in food which induces a unique flavor [3] & [4]. Generally, MSG is considered a safe food additive. However, inadvertent abuse of this compound may occur due to its abundance, mostly without labeling in many food ingredients that may lead to toxic effect to human and experimental animals [5] & [6]. It could produce symptoms such as numbness, weakness, flushing, sweating, dizziness and headaches. In addition, ingestion of MSG has been alleged to cause or exacerbate numerous conditions, including asthma, urticaria, atopic dermatitis, ventricular arrhythmia, neuropathy and abdominal discomfort [7].

Oxidative stress is considered as the mechanism of MSG induced toxicities [8]. It occurs due to imbalance between reactive oxygen species (ROS) production and endogenous antioxidant defense mechanisms [9].

Flavonoids are polyphenolic compounds mainly included in natural plants and are used currently for various kinds of foods and beverages as antioxidant additives [10]. Their beneficial effects against degenerative process linked to ageing or oxidative stress, such as cancers or cardiovascular diseases are now well documented [11]. They may scavenge ROS, chelate metal ions, act as chain-breaking antioxidants by scavenging lipid peroxil radicals, or integrate into the lipid bilayer to prevent lipid damage [12].

Quercetin (3,3′,4′,5,7-pentahydroxyflavone), a polyphenolic flavonoid compound is a powerful bioactive constituent of the human diet as a free radical scavenging agent [10]. Quercetin has many beneficial effects such as cardiovascular protection, anticancer activity, antiallergic activity, antiviral activity and anti-inflammatory effects [13].

II. Aim of the Work

The aim of the current work is to evaluate toxic effect of MSG on the heart and the role of quercetin on alleviation of this toxicity in adult albino rats.

III. Materials and Methods

3.1. Chemicals:

Monosodium glutamate (MSG) powder of purity ≥ 99% was brought from Sigma-Aldrich, Inc. (3050 Spruce Street, Saint Louis, MO 63103, USA), CAS Number: 142-47-2, it was dissolved in distilled water before usage, 1 gm of MSG in 1 ml of distilled water [14]. Quercetin powder of purity ≥ 95% was purchased from Sigma-Aldrich Chemical Co. 3050 Spruce Street, Saint Louis, MO 63103,USA), CAS Number: 849061-97-8, it was dissolved in distilled water and given orally by gastric intubation at dose 50 mg/kg body weight [15]. Distilled water was purchased from Misr Chemical Industries Co, Cairo, Egypt.

3.2. Experimental animals and treatment:

Fifty adult albino rats weighing 180-200 g were obtained from the animal breeding house of Faculty of veterinary medicine, Moshtohor, Banha university. At the beginning of the study, they were acclimatized for one week in a fully ventilated room at Department of anatomy, Faculty of Medicine, Banha University. Rats were allowed free access to balanced diet and distilled water. All experiments were carried out in accordance with the research protocols according to the Ethics Committee of Scientific Research, Faculty of Medicine, Banha University which followed the recommendations of the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985).

At the beginning of the experiment; fifty adult albino rats were equally divided into five groups (10 per each) as follows:

Group 1 (negative control group): they were allowed to free access to balanced diet and water till the end of the experiment to evaluate the standard parameters.
Group 2 (positive control group): treated with 1ml of distilled water (solvent) as a single dose, by gastric gavage tube for 45 days.
Group 3 (quercetin treated group): Each rat was given quercetin dissolved in distilled water at a dose of 50 mg/kg orally once daily for 45 days.
Group 4 (MSG treated group): each rat was received MSG dissolved in distilled water at dose 4g /kg/day as a single dose, orally for 45 days.
Group 5 (MSG + quercetin treated group): each rat was given quercetin at a dose of 50 mg/kg/day orally half an hour before giving MSG at a dose of 4g/kg/day as a single dose, orally for 45 days.

3.3. Sample preparation:

3.3.1.Blood sample:

At the end of the experiment, the animals were anaesthetized by light ether after being fasted for 6 hours, and while the heart was still beating, blood samples (5 mL) were collected from abdominal aorta in dry test tubes and allowed to coagulate at room temperature for 30 minutes. Serum was separated by centrifugation at 2500 rpm for 10 minutes using centrifuge 5418R (Eppendorf, Ontario, Canada) to separate the serum, then it was stored at -20 Co for biochemical analysis of cardiac troponin I (cTn1) enzyme level and the activity of creatine kinase MB (CK- MB) enzyme.

3.3.2.Tissue sample:

After taking of blood sample, the animals were sacrificed by decapitation; the thorax was opened using ventro-median incision between the jugular notch and the xiphoid process. The heart was immediately excised and stripped off from paraaotic fat and fascia, then it was dissected into two halves, one half is stored in 10% neutral formalin for histopathological examination, and the other half is stored at (−80°C) for assessment of oxidative stress markers*;* tissue malondialdehyde level (MDA) glutathione-s- transferase (GST).

3.4. Studied parameters:

3. 4. 1. Serum biochemical parameters

The collected serum was used for estimation of The cardiac marker enzymes; cardiac troponin I (cTnI) level using commercially available enzyme immunoassay kits (DRG International Inc., USA) and creatine kinase- MB (CK-MB) activity was estimated respective kit from Diamond Diagnostics (Cairo, Egypt). They were expressed by (ng/ml & IU/L respectively).

3.4.2. Tissue biochemical oxidative stress parameters (MDA & GST)

About 100 mg of heart tissue were homogenized in 2 mL of an ice-cold buffer composed of 50 mmol/L potassium phosphates, 1 mmol/L EDTA, pH 7.5, using a mortar and pestle. The homogenate was then centrifuged for 15 min at 4°C, and the resultant supernatant was kept at -20°C until analysis. The oxidative stress markers malondialdehyde (MDA) which is a marker of lipid peroxidation & Glutathione-S- transferase

(GST) which is an antioxidant) were analyzed using a colorimetric method according to the manufacturer's instructions (Bio diagnostics, Dokki, Giza, Egypt). MDA were expressed by (nmol /g tissue) & GST by (u/g).

3.4.3. Histopathological Examination

The heart of each rat was immediately washed with saline, and then fixed in neutral buffered formalin (10%). The fixed tissues were embedded in paraffin, and then serial sections of 5 μm thickness were cut. Each section was stained with hematoxylin and eosin (H & E), and examined under light microscope according to [16], at pathology department, faculty of medicine, Banha university.

3.4.5. Statistical analysis

Software (SPSS, Version 20.0 for Windows, SPSS Inc., Chicago, IL) was used for the univariate, bivariate, and stratified analyses of the data. Kruskal-Wallis was used for multiple comparisons of quantitative variables and Man-Whitney test was applied for the comparison of quantitative variables after establishing their non - normality by K-S test of normality. ANOVA test was used for comparing means of parametric variable with using post hoc test (LSD) for multiple comparisons. Differences were considered significant at $P \leq .05$.

IV. Results

Treatment of rats with quercetin alone (quercetin group) did not illustrate any significant variation in the whole parameters evaluated when compared to untreated control groups ($P > 0.05$), indicating the non-toxic nature of quercetin.

4.1. Effect of quercetin on cardiac marker enzymes in the serum:

Chronic oral administration of MSG leading to significant increased in the activity of cardiac function markers in serum; creatine phosphokinase (CK-MB) & cardiac troponin I (cTnI) as compared to both control groups ($P < 0.001$), whereas co-supplementation of quercetin with MSG exhibited a significant reduction in level of these cardiac marker enzymes compared to the MSG-treated group ($P < 0.001$) denoting its protective role in MSG induced cardiotoxic effects as shown in table 1 & fig.1.

4.2. Effect of quercetin on oxidative stress parameters level in the cardiac tissue:

Lipid peroxidative markers, as determined by MDA formation was found elevated significantly in the cardiac tissue of MSG-treated rats compared to control ($P < 0.001$). A markable recovery was observed in rats treated with quercetin along with MSG in form of marked significant reduction in cardiac MDA induced by MSG as illustrated in table1 & fig.2.

A significantly decreased activity of GST was observed in the MSG-induced group. Further, simultaneous administration of quercetin prior to the administration of MSG significantly increased the activity of GST compared to MSG treated group alone as showed in table1 & fig.2.

4.3. Histopathology of heart:

No histopathological alterations were observed in control group or quercetin treated rats. sections of cardiac tissue of control and quercetin treated animals showed normal striated cardiac muscle fibers with spindle shaped nuclei fig.3 (A).

sections of cardiac tissues of MSG-induced rats showed cloudy swelling, fiber separation, vascular congestion and inflammatory cell infiltrate fig.3 (B1 & B2).

Concomitant administration of quercetin along with MSG modulated the previously mentioned cardiac histopathological changes fig.3 (C).

Table (1): Statistical Comparison between the study groups according to The cardiac marker enzyme; creatine kinase- MB (CK-MB) & cardiac troponin I (cTnI), tissue oxidative stress parameters malondialdehyde (MDA) & Glutathione-S- transferase (GST).

	Negative Control group	Positive control group	Quercetin group	MSG group	Quercetin + MSG group	Test	P value
CKMB Median (IQR)	524.74 (497.48-531.7)	529.61 (514.59- 540.64)	530.75 (525.43-534.68	2463.84.84*†‡ (2301.85-2667.14)	772.43$^{*\dagger\ddagger\Delta}$ (748.28-832.17)	KW= 38.34	<0.001 **
Troponin Median (IQR)	26.5 (25.0-28.0)	26.5 (22.75-27.25)	24.5 (23.0-28.25)	84.5*†‡ (82.0-88.25)	41.5$^{*\dagger\ddagger\Delta}$ (38.75-44.25)	KW= 38.44	<0.001 **
Tissue MDA Median (IQR)	37.5 (35.0-39.5)	37.5 (34.75- 41.75)	37.5 (34.75-43.25)	93.0*†‡ (88.75-95.25)	56.0$^{*\dagger\ddagger\Delta}$ (52.75-59.25)	KW= 37.8	<0.001 **
Tissue GST Median (IQR)	6.81 (5.0-8.69)	7.18 (4.97-8.25)	7.18 (4.97-8.25)	2.5 *†‡ (1.8-2.93)	6.64$^{\Delta}$ (4.22-8.51)	KW= 23.65	<0.001 **

(**) = Highly significant P (<0.001); ±SD: standard deviation; F test: ANOVA; IQR→ Interquartile range, Kruskal -Wallis test;

*→ Significant versus Negative Control group.
‡→ Significant versus Quercetin group.
†→ Significant versus Positive control group.
Δ→ Significant versus MSG group.

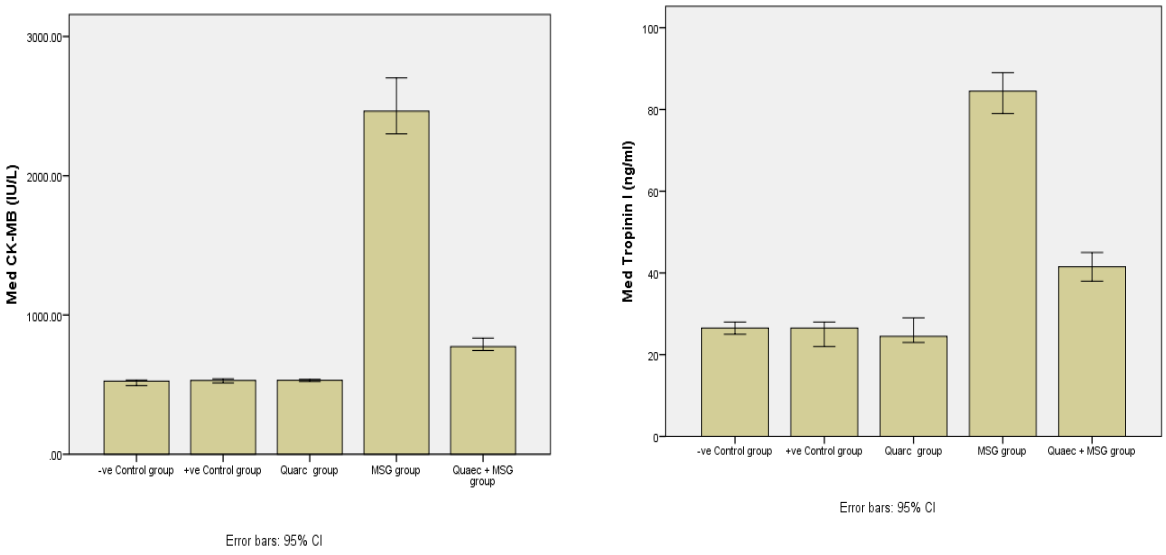


Fig. (2): Bar chart showing comparison between the studied groups regarding the effect of quercetin (Querc) on MSG-induced alteration in cardiac function markers in serum: creatine phosphokinase (CK-MB) & cardiac troponin I (cTnI).

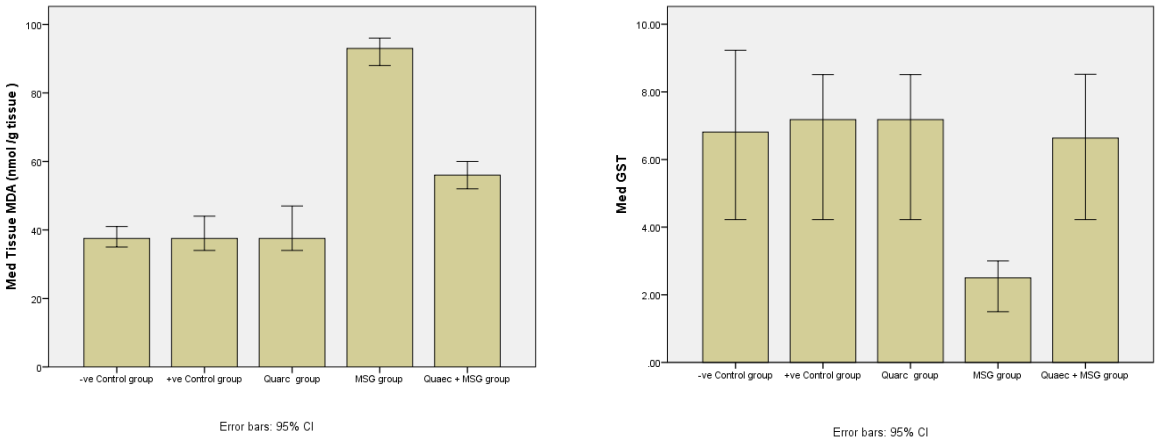


Fig. (3): Bar chart showing comparison between the studied groups regarding the effect of quercetin (Querc) on MSG-induced alteration in oxidative stress parameters in cardiac tissue: malondialdehyde (MDA) & Glutathione-S- transferase (GST).

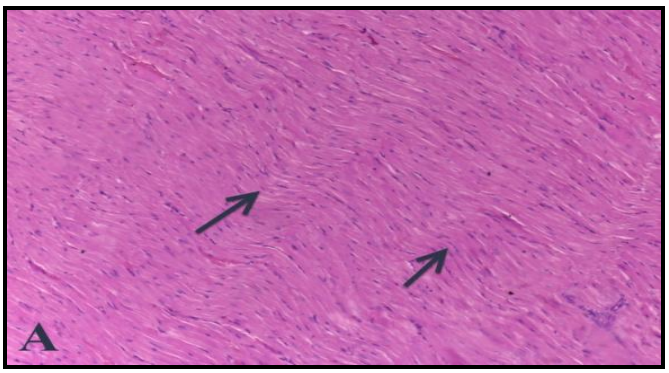
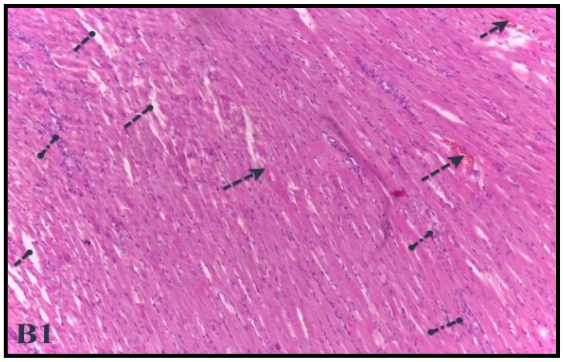


Fig. (3A): Light microscopic photographs from sections of cardiac tissue of control rat showed normal striated cardiac muscle fibers with spindle shaped nuclei (⟶) (H&E, ×200).



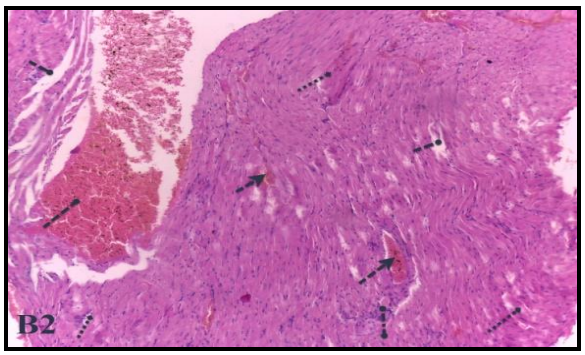


Fig. (3B1&B2): Light microscopic photographs from sections of cardiac tissue of MSG-treated rat heart muscle fibers illustrated cloudy swelling with evidence of fiber separation (▬▬▬➔) and vascular congestion (▬▬➔)& hemorrhage(▪▪▪▪♦)& inflammatory cell infiltrate (H&E, ×200).

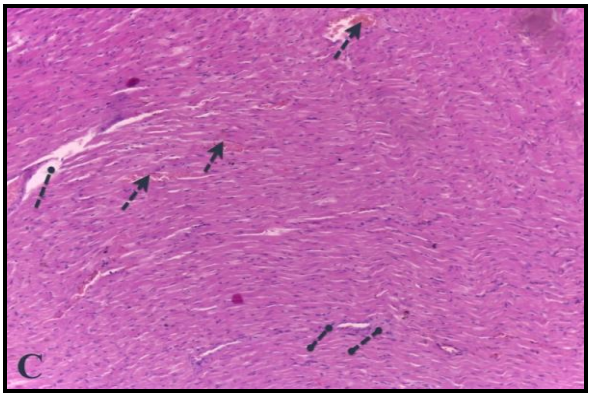


Fig. (3C): Light micrographs from sections of cardiac tissue of rats with concomitant administration of quercetin alon with MSG showed reduced swelling (▬▬▬➔)and no indication of fiber separation, vascular congestion (▬▬➔) & inflammatory cell infiltrate (●▪▪▪▪▪●) (H&E, ×200).

V. Discussion

Although, MSG was thought to be safe at the time of its discovery as it is a natural substance [17], but in fact many studies concluded that its utilization has been linked with many toxic metabolic effects in many tissues such as the liver, kidney, and brain [18]. However, unusual effects on the cardiovascular system have been described [17].

The results of this study revealed an increase in activity of cardiac enzyme (CK-MB), and an increase in serum cardiac troponin I (cTnI) levels in MSG treated rats as compared with control.

These results are in line with the study of [19]. that showed significant increase in CK-MB & cTnI in MSG treated rats in low and high doses as compared with control. Also, [20] have showed similar elevation in serum CK-MB activity in rats treated with MSG.

[21] revealed that, there were marked elevation in the levels of cardiac enzymes AST, ALT, LDH, CK and cTnI in serum of rats after intraperitoneal injection of them with MSG compared to normal control rats.

The elevations in cardiac markers (CK-MB & cTnI) might be attributed to ample concentrations of these diagnostic markers of myocardial damage that is released into the extracellular fluid once myocardial cells are damaged [22].

The present study showed a significant increase in MDA which is a marker of lipid peroxidation in MSG treated rats. While, there was a significant reduction in GST activity in these rats as compared with control.

Obtained results are in agreement with [20] who recorded an elevation of MDA and reduction in activities of superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), and GSH related enzymes such as GST and glutathione peroxidase (GPX) which protect the heart from oxygen derived free radicals.

Also, [23], reported that increased lipid peroxidation (LPO) products, MDA and decrease in the levels of SOD, GSH and GPx after oral administration of MSG in rats.

The histopathological results in the current study showed cloudy swelling with fiber separation, hemorrhage, and congestion of cardiac tissue in MSG treated rats in comparison with control rats. [20] and [16] had noticed similar histopathological findings in their studies.

The cardiotoxic effects of MSG are thought to be mediated through the glutamate receptors, as Continuous stimulation of metabotropic glutamate receptors may induce osmotic damage and produce oscillatory increase or intracellular mobilization of calcium stores leading to Ca^{2+} homeostasis imbalance which trigger the activation of several enzyme pathways and signaling cascades such as calmodulin, phospholipases, protein kinases, proteases, protein phosphatases and nitric acid synthases and leads to production of several free radicals [24] & [25].

MSG had the capacity to induce oxidative stress by increasing the lipid peroxidation and decreasing the activity of antioxidant defense systems in the cardiac tissue [20] & [26]. **(**After treatment of rats with quercetin + MSG, there were reduction of MDA, elevation of GST activity in cardiac tissue, restoration of normal cardiac markers CK-MB & cTnI, and improvement of histological changes of cardiac tissue nearly return to normal.

These findings are greatly in accordance with [27] who reported reduction in both SOD and GPx in rats treated with MSG and significant amelioration in these antioxidant enzymes after combination with Quercetin.

The results of current work are in agreement with those of [28]**,** who stated that quercetin, a potent anti-oxidant defense pathway in vivo and vitro. [29] also concluded that a low dose of chlorpyrifos causes testicular toxicity in adult male rats that can be ameliorated with antioxidants catechin and quercetin.

The improvement occurred after quercetin combination with MSG may be explained by the antioxidative properties of quercetin which alter peroxidation kinetics by modification of the lipid packing order and to decrease fluidity of the membrane. These changes could carefully hinder the diffusion of free radicals and restrict their peroxidative reactions [30].

VI. Conclusion

To end up with conclusion, the results of the present study revealed that the chronic oral exposure to high doses of MSG has a deleterious effect on the heart which leads to cardiac dysfunction. Supplementation of quercetin along with MSG ameliorated lipid peroxidation, increased antioxidant activities and prevents oxidative damages. Thus even at a higher level of MSG exposure quercetin can exert a protecting role against MSG induced cardiotoxicity in adult albino rats.

VII. Recommendations

1- Restriction of MSG usage as a flavoring enhancer additive in foods to a very small amount under the supervision of health authorities.
2- People should be aware of the adverse effects of MSG & control their intake of MSG added foods.
3- Quercetin can exert an alleviating effect on MSG induced cardiotoxicity. Thus, high consumption of quercetin rich food (vegetables & fruits containing polyphenolic flavonoid) along with MSG suspected food are recommended.
4- Further investigative studies about the protective effect of quercetin and other flavonoid on toxic effect of MSG on different organs should be done.

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