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RESEARCH ARTICLE

Evaluate the protective effects of some antioxidant agent (β-carotene and Curcumin) against Monosodium Glutamate-induced cardiopathy in male albino rats.

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Abstract

Cardiovascular disease (CVD) is a major factor of morbidity and mortality in adult man. This study was designed to evaluate the protective effect of β-carotene and curcumin against Monosodium Glutamate induced cardiotoxicity in 40 male albino rats (weighing 150-200 g) divided into four groups, each of ten rats. The GI (Control) injected intraperitoneally with distilled water (0.6ml) three times weekly for three weeks; GII (MSG) was injected intraperitoneally with 4g/ kg/day of MSG. The GIII (β carotene + MSG) and GIV (Curcumin + MSG) were pretreated with β carotene (10mg /kg) and curcumin (60mg/kg) respectively by injected intraperitoneal three times weekly for three weeks one hour before MSG injection.

Results showed significant ($p<0.01$) increase in the activity of AST, ALT, LDH, CK and cTnI in serum compared with normal control rats and after pretreatment with β carotene (10mg/kg) and curcumin (60mg/kg) three times weekly for three weeks show significantly ($p<0.01$) decrease the activity of these enzymes compared to MSG injected alone in rats but there is still significant ($P<0.01$) increase in comparison with the normal rats.In homogenate heart tissues, showed considerable ($p<0.01$) decrease in the levels of GSH and SOD and increases in the levels of MDA after rats injected with MSG compared to normal control rats three times weekly for three weeks. Pretreatment with β carotene and curcumin separately to MSG-injected rats caused significantly ($p<0.01$) increased the levels of GSH and SOD compared to MSG injected alone in rats but there is still significant ($P< 0.01$) decrease in comparison with the normal rats. However, it showed significant ($p<0.01$) decreases in the levels of MDA compared to MSG injected alone and still significant ($P< 0.01$) increases in comparison with the normal rats.

Histopathological examination of H&E stained sections of the hearts, show normal histological features of cardiac fibers in the control group (GI). After MSG injected rats showed histopathologic changes were expressed as a focal area of coagulative necrosis of the myocardium and Karyopyknosis, hypereosinophilia and loss of striation were shown in myofibers, also, detected infiltration of macrophage in the interstitium and congestion of blood vessels can be observed. However, examination of Hx&E stained sections of the hearts of the rats pretreated with β carotene before MSG injection revealed only congestion of blood vessels with normal myofiber and the pretreated with curcumin before MSG injection showed congestion of blood vessels with more or less normal myocardial fibers.

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Introduction:-

Cardiovascular deceases (CVD) remained one of the main causes of death all over the world and several developing countries .CVD, is the most common form of heart disease, CAD is a disease affecting the arterialblood vessel and is commonly referred to ashardening or furring" of the arteries. It is caused by formation of multiple plaques within the arteries[1,2,3].

Monosodium glutamate (MSG) is asubstance widely used as flavoring agent in the wholeworld. It is the sodium salts of glutamic acid, it isadded to the food either as a purified monosodiumsalt or as a component of a mixture of amino acidsand small peptides resulting from the acid or enzymatic hydrolysis of proteins[4].When it is added to food in relatively small quantities ,the palatability of this food increases[5]. MSG is absorbed very quickly from gastrointestinal tract and could spike blood plasma level of glutamate[4]. Glutamate is the most abundant amino acidin the central nervous system where it functions as anexcitant neurotransmitter. It is especially highly concentrated in those regions of the brain that areessential in cognitive processes mediation; in the cerebral cortex, hippocampal gyrus dentatus and striatum[6].

Antioxidants may be molecules that can neutralize free radicals by accepting or donating electron(s) to eliminate the unpaired condition of the radical. The antioxidant molecules may directly react with the reactive radicals and destroy them, while they may become new free radicals which are less active, longer-lived and less dangerous than those radicals they have neutralized. They may be neutralized by other antioxidants or other mechanisms to terminate their radical status[7]. Many antioxidants may directly react with reactive oxygen species (ROS) and/or free radical intermediates induced by ROS and terminate the chain reaction, thereby stopping the ROS-induced damage[8,9,10].Another important function of antioxidants is to regulate ROS-related enzymes. Antioxidants may decrease the cellular level of free radicals either by inhibiting the activities or expressions of free radical generating enzymes such as xanthine oxidase (XO) or by enhancing the activities and expressions of antioxidant enzymes such as superoxide dismutase (SOD), glutathione reductase (GRd), glutathione S-transferase (GST) and thioredoxin reductase (TrxR)[11]. These antioxidant enzymes produced in the body provide an important defense against free radicals[12].

Higher plasma carotenoids at baseline have been associated with significant reductions in the risk of cardiovascular disease in some prospective studies[13]but not in others[14]. It is not yet clear whether this effect is a result of carotenoids or other factors associated with diets high in carotenoid-rich fruits and vegetables. In contrast, four randomized controlled trials found no evidence that beta-carotene supplements in doses ranging from 20 to 50 mg/day were effective in preventing cardiovascular diseases[15].

Curcumin ($C_{21}H_{20}O_6$), a yellow pigment is found in the rhizome of *Curcuma loga*, also known as turmeric, has been used since ancient times in China to treat a variety of digestive and neuropsychiatric disorders[16].Curcumin has an ability to scavenge various types of ROS; curcumin can decrease oxidative damage of proteins, lipids and DNA as reported in multiple studies[17]. Curcumin is also shown to augment the activities of antioxidant enzymes, such as superoxide dismutase (SOD), catalase, reduced glutathione (GSH), glutathione S transferase (GST) and glutathione peroxidase (GPx)[18]. Since increased oxidative stress is associated with various cardiovascular diseases and ROS are also known to induce pro-inflammatory responses, the inhibitory effect of curcumin on ROS generation coupled with its anti-inflammatory properties may contribute towards its protective role in cardiovascular diseases[19].

Curcumin decreased the incidence of future heart attacks by over two and half times compared to patients not receiving any curcumin. Furthermore, the incidence of left ventricular dysfunction (a measure of the damage to the heart was significantly reduced again in the curcumin group, this time by nearly nine times. Other biological markers of heart disease such as inflammation (C - reactive protein, CRP) were also greatly reduced[20]. It may thus be suggested that the ability of curcumin to reduce oxidative stress and attenuate pro-hypertrophic and pro-inflammatory responses may play an important role in reducing cardio-toxicity and hypertrophy in various experimental models[21,22].

So**,** the aim of the present study to evaluate the cardioprotective effects of different antioxidants (curcumin and β carotene) on biochemical and histological changes that may occur in rat's hearts after injected with of MSG.

Materials and methods:-

Forty adult male albino rats (150 to 200g) were brought from animal house, Faculty of Medicine, Assiut University, Assiut, Egypt, and were maintained on a balanced diet with free water supply in clean containers. They were kept for two weeks under this condition to adapt the laboratory conditions before the start of the experiment. All animals were fasted for 1 hour prior to drug administration.

Experimental Design:-

Rats were divided into four groups, each of ten rats as follows:

Group I (Control group), rats were injected intraperitoneal with distilled water (0.6ml) three times weekly for three weeks.

Group II (MSG), MSG cardio-toxicity was induced rats by intraperitoneal injection (4 mg g^{-1} b.wt.) three times weekly for three weeks[23,24.]

Group III (β carotene+ MSG)MSG injected rats pretreated with βcarotene (10mg/kg) by injecting intraperitoneally three times weekly for three weeks one hour before MSG injection[25]**.**

Group IV(Curcumin +MSG), MSG injected rats pretreated with curcumin (60mg/kg) by injected intraperitoneally three times weekly for three weeks, one hour before MSG injection[26]**.**

Drugs and chemicals:-

MSG, β carotene and Curcumin werepurchased from Sigma chemical company (Aldrich, USA) and dissolved in distilled water before administration. AST, ALT and LDH kits were purchased from Vitro Scient- Egypt and GSH, SOD and MDA kits were purchased from Bio-diagnostic - Egypt. While CK kitwas purchased from ChemaDiagnostic- Italy and CTnI kitwas purchased fromMonobind Inc. - USA.

Sample Preparation:-

At the end of the experimental period, animals of different experimental groups were fasted overnight (12-14 h), all the rats were anesthetized with ether and sacrificed by cervical decapitation. Blood was collected from carotid artery into a dry clean graduated glass centrifuge tube. It was rapidly set to centrifuge at 5000 rpm for 10 minutes and the serum was separated and kept in clean stopper plastic vial at –80°C until the analysis of serum parameters.

After decapitation, the hearts were rapidly dissected out and washed immediately three times with saline and blotted on filter paper. Specimens from each experimental group were swiftly separated into two pieces, one for tissue homogenates and the other for histopathological examination.

Biochemical analysis:-

Serum AST and ALT activities were determined by enzymatic colorimetric method[26] by using commercial kit that was supplied by Vitro Scient (Egypt). Serumlactate dehydrogenase level was estimated by enzymatic– colometric method[27] using commercial kit that was supplied by ChemelaxIndustria, Barcelona, Spain. Serum creatine kinase (CK) was done by enzymatic– colometric method by using commercial kit that was supplied by ChemaDiagnostica Company -Italy. The level of CK was estimated according to the method of **Bergmeyer**[28]. Serum level of Troponin-I (CTnI) was done by Immunoenzymometric assay [29]Monobind Inc. –USA.

The levels of reduced glutathione (GSH), superoxide dismutase (SOD) and Malondialdehyde (MDA) in the heart tissues homogenate was estimated by colorimetric method by using commercial kit that was supplied by Bio-diagnostic, Egypt.Thelevels ofGSH, MDA and SOD were determined according to the methods described[30,31,32]respectively**.**

Preparation of tissue homogenates:-

One piece from each experimental group were weighted and homogenized separately with a tissue homogenizer. The tissue homogenate was centrifuged at 11,739 rcf, for 15 min in a refrigerated centrifuge and the supernatant was used for the different analysis[33]**.**

Histopathological Examination

Heart tissue was fixed in 10% neutral buffered formalin. After fixation, specimens were dehydrated, cleared, embedded in paraffin, prepared as 5-µm-thick sections and stained with Hematoxylin and Eosin (H&E) as a routine method after **Upaganlawar*et al.*[34].** All stained slides were viewed under a light microscope to assess the histopathological examination.

Results:-

The control rats appeared healthy and no mortality was recorded, whereas two rats died in MSG injected untreated rats, one rat died in MSG injected rats pretreated with β carotene and two rats died in MSG injected rats pretreated with curcumin.

Rats injected with MSG showed significant ($p<0.01$) increase in the activity of AST, ALT, LDH, CK and cTnIin serum compared to normal control rats. pretreated with β carotene (10mg /kg) and curcumin (60mg/kg) by injected intraperitoneal three times weekly for three weeks one hour before MSG injection, significantly ($p<0.01$) decrease the activity of this enzyme compared with MSG injected alone in rats but there is still significant ($P<0.01$) increase in comparison with the normal rats. There is no significant ($P>0.05$) difference between βcarotene and curcumin in their effects on the activity of this enzyme (Table 1)

Rats injected with MSG showed considerable ($p<0.01$) decrease in the levels of GSH and SOD in the heart compared to normal control rats. Pretreatment with β carotene (10mg/kg) and curcumin (60mg/kg) by injected intraperitoneal three times weekly for three weeks one hour before MSG injection rats significantly ($p<0.01$) increased the level of GSH compared with MSG injected alone in rats but there is still significant ($P< 0.01$) decrease in comparison with the normal rats. There is no significant ($P> 0.05$) difference between β carotene and curcumin in their effects on the levels of GSH (Table 2)

Rats injected with MSG showed significant ($p<0.01$) increase in the level of (MDA) in the heart compared to normal control rats. Pretreatment with β carotene (10mg/kg) and curcumin (60mg/kg) by injected intraperitoneal three times weekly for three weeks one hour before MSG injection significantly ($p<0.01$) decreased the level of MDA compared with MSG injected alone in rats but there is still significant ($P< 0.01$) increase in comparison with the normal rats. There is no significant ($P> 0.05$) difference between β carotene and curcumin in their effects on the levels of MDA (Table 2)

Table (1): Effect of pretreatment with β carotene and curcumin on the serum of AST (U/l), ALT (U/l), LDH (IU/l), CK (IU/l) and cTnI (ng/ml) after MSG-induced cardiomyopathy in adult male rats.

Groups / parameters	GI (Control)	GII (MSG)	GIII (β carotene+ MSG)	GIV (Curcumin+ MSG)
AST (IU/l)	34.02±2.24	**60.57±2.81[a]**	**49.32±2.82[ab]**	**47.23±2.4 8[ab]**
ALT (IU/l)	**24.48±2.62**	**53.31±2.28[a]**	**40.59±4.19[ab]**	**37.88±2.36[ab]**
LDH (IU/l)	**80.98±3.63**	**163.03±2.20[a]**	**105.07±4.02[ab]**	**95.13±3.26[ab]**
CK (IU/l)	**165.76±4.56**	**282.47±8.57[a]**	**197.06±6.96[ab]**	**192.60±3.88[ab]**
cTnI (ng/ml)	**0.160± 0.03**	**2.37±0.017[a]**	**1.12±0.051[ab]**	**0.98±0.049[ab]**

Each value represents the mean ± SE (standard error).
a Significant difference from the control normal (GI) rats ($P<0.01$)
b Significant difference from untreated MSG(GII) rats ($P<0.01$).

Table (2): Effect of pretreatment with β carotene and curcumin on cardiac tissues of GSH (mmol/g tissue), SOD (U/g tissue) and MDA (nmol/g tissue) after MSG-induced cardiomyopathy in adult male rats.

Groups / parameters	GI (Control)	GII (MSG)	GIII (β carotene+ MSG)	GIV (Curcumin+MSG)
GSH (mmol/g tissue)	**11.62±0.80**	**3.90±0.37[a]**	**8.40±0.78[ab]**	**9.04±0.50[ab]**
SOD (U/g tissue)	**17.47±1.30**	**6.01±0.63[a]**	**11.20±1.01[ab]**	**11.93±0.91[ab]**
MDA (nmol/g tissue)	**1.04±0.18**	**2.65±0.20[a]**	**1.52±0.19[ab]**	**1.70±0.12[ab]**

Each value represents the mean ± SE (standard error).
a Significant difference from the control normal (GI) rats (P<0.01)
b Significant difference from untreated MSG(GII) rats (P<0.01).

Control sections of hearts revealed normal histological features of cardiac fibres (Fig.1). After examination of Hx&E stained sections of the hearts of MSG injected rats showed histopathologic changes were expressed as focal area of coagulative necrosis of the myocardium (Fig.2a). The myofibers show Karyopyknosis, hyper eosinophilia and loss of striation (Fig.2b).Infiltration of macrophage in the interstitium (Fig.2c). Congestion of blood vessels can be observed (Fig.2d).

However, examination of Hx& E stained sections of the hearts of the rats pretreated with β carotene before MSG injection revealed only congestion of blood vessels with normal myofibres (Fig.3a&b)

Also, examination of Hx& E stained sections of the hearts of the rats treated with curcumin before MSG injection showed congestion of blood vessels with more or less normal myocardial fibers (Fig.4a&b)

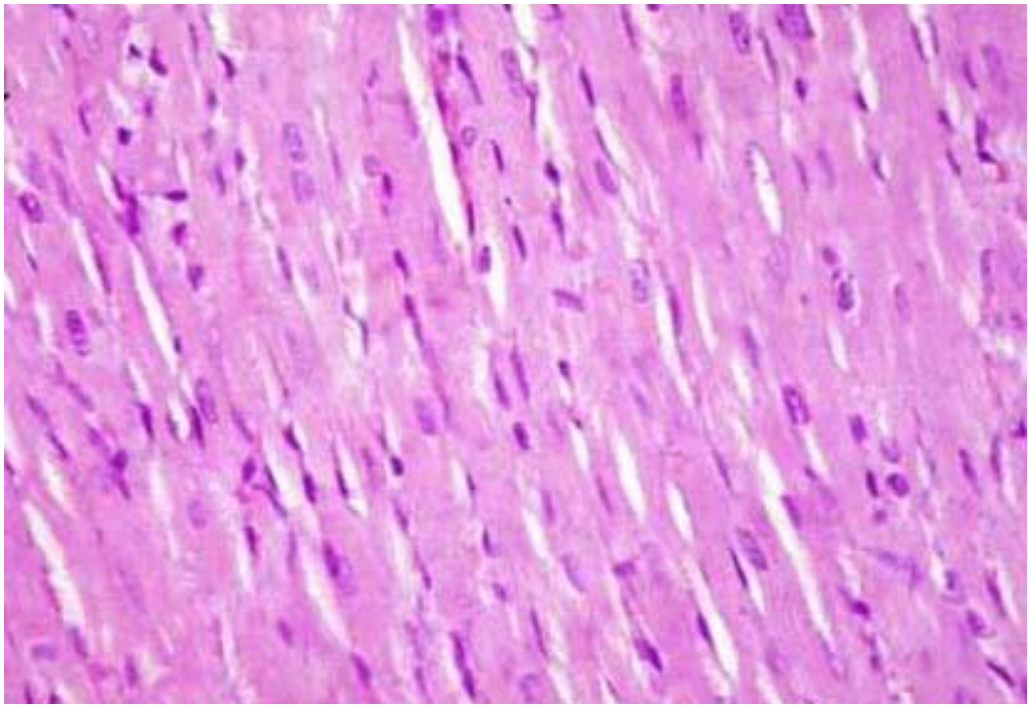

Fig.1: A photomicrograph of a section of normal Albino rat's heart showing its normal stracture of myocardium with its normal muscle fibers (Hx&E).

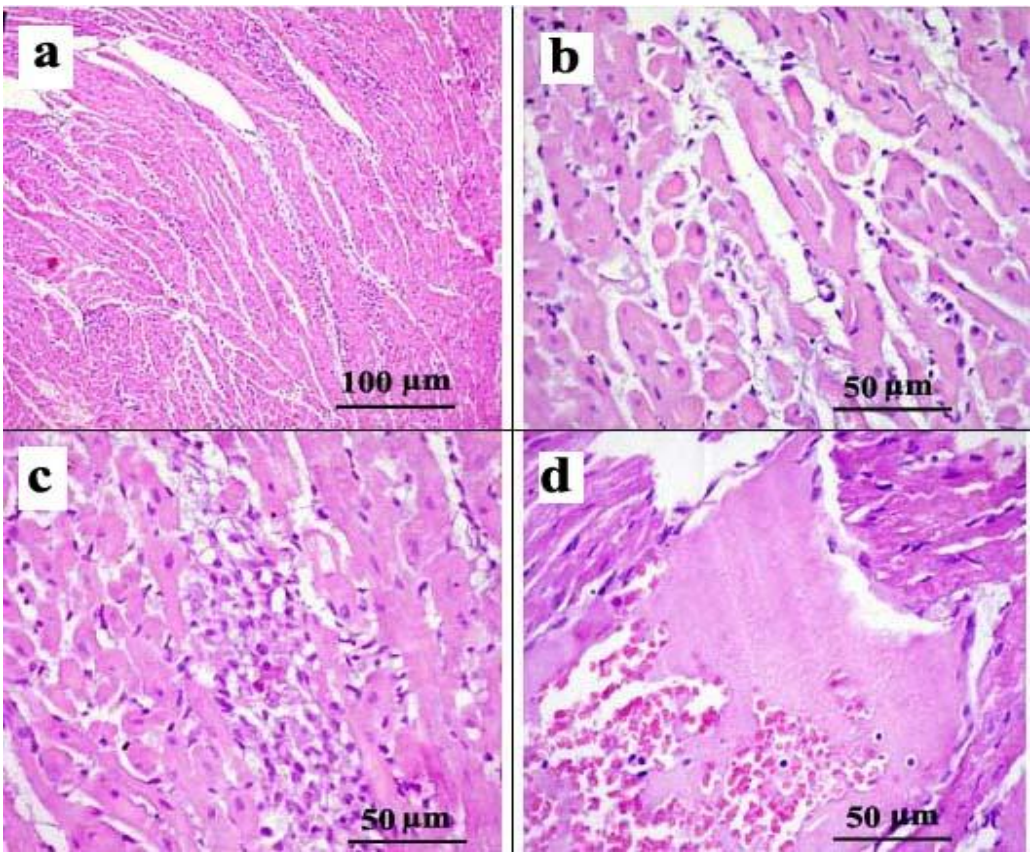

Fig.2: A photomicrograph of hearts section of MSG injected rats show focal area of coagulative necrosis of the myocardium (a), pyknosis and leukocytic infiltration (b), infiltration of macrophage in the interstitium (c) and congestion of blood vessels (d). (Hx&E).

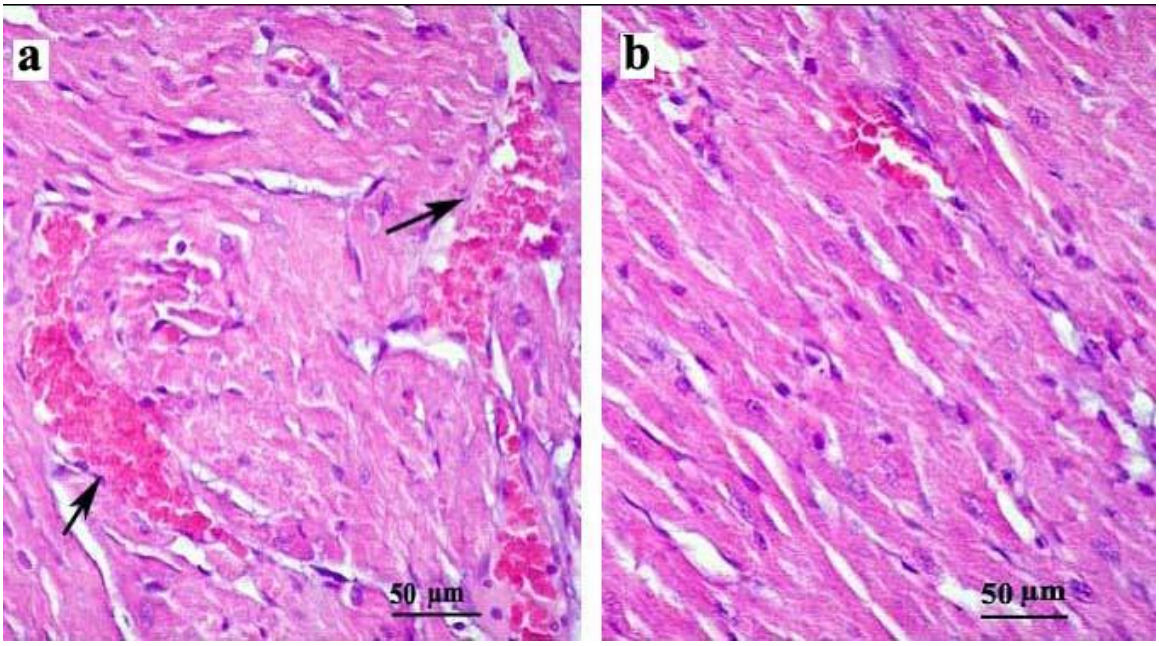

Fig.3: A photomicrograph of hearts section of rats pretreated with β carotene before MSG injection showing (a) congestion (arrow), (b) normal myofibers and congestion.

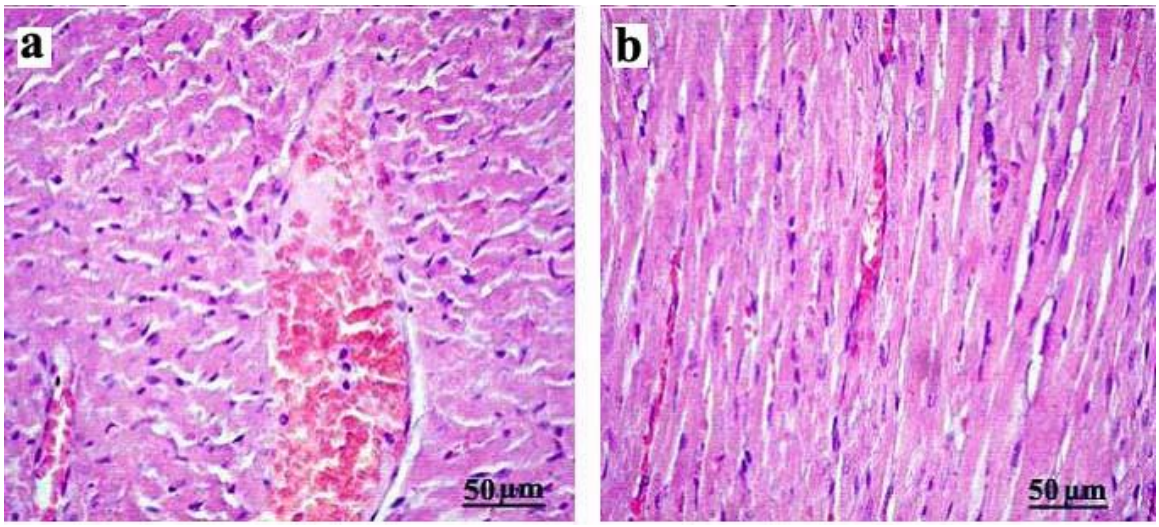

Fig.4: A photomicrograph of the hearts section of rats pretreated with curcumin before MSG injection showing congestion of blood vessels with more or less normal myocardial fibers (a&b)

Discussion

Currently, MSG is frequently used as a flavor enhancer, the fact of which makes it one of the most applied food additives in the modern nutrition all over the world[35].

In the present study, after intraperitoneal injection of rats with MSG showed marked elevation in the levels of cardiac marker enzymes, AST, ALT, LDH, CK and cTnI in serum compared to normal control rats. These results were in agreement with the results obtained by **Robbins and Cotran**[36]**and Sauganth Paul *et al.***[37] who proved that chronic oral administration of MSG caused oxidative stress that was manifested by significant increase in the serum levels of aspartate transaminase, creatine phosphokinase and lactate dehydrogenase suggested a cardiac functional disorder.

Abdel Baky*et al.* [19] suggested that oxidative cardiac tissue damage induced by toxic effect of MSG in rats was ensured by pronounced increased the serum levels CPK and AST.It is well known that marker CK, AST, ALT and LDH are well known markers when myocardial cells are damaged or destroyed are due to deficient oxygen supply or glucose, the cardiac membrane becomes permeable or may rupture which results in leakage of enzymes which enter into the blood stream, thus increasing their concentration in the serum[38,39,40].

Data of present study showed that intraperitoneal injection of MSG lead to decreased cardiac reduced glutathione (GSH) level, **superoxide dismutase** (SOD) level and increase malondialdehyde (MDA) level in heart tissues. The obtained results are in line with the results of **Singh and Pushpa**[23]**, Farombi and Onyema**[24] and **Paul *et al.***[43] they found that chronic oral administration of MSG causes oxidative stress which is manifested by significant increase in levels of lipid peroxidation as evidenced by increased levels of MDA in the heart and by the decrease in superoxide dismutase, reduced glutathione, glutathione peroxidase and glutathione S-transferase in cardiac tissue

Also, **Kuldip and Singh**[41] reported that oral administration of MSG increase lipid peroxidation (LPO) products, MDA and decrease in the levels of SOD, GSH and GPx.Lipid peroxidation, a type of oxidative deterioration of polyunsaturated fatty acids has been linked with altered membrane structure and enzyme inactivation. Lipid peroxidation is associated with a variety of chronic health problems, such as cancer, ageing and atherosclerosis[42].

In addition, effects of MSG may be related to an imbalance between the oxidant and antioxidant systems. This was indicated by marked increased levels of serum nitric oxide (NO) accompanied by pronounced increased level of thiobarbituric acid reactive substances (TBARS, marker of lipid peroxidation) and decreased levels of the antioxidants, L-ascorbic acid, glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT) in cardiac tissue [19].

After treatment with β carotene significantly decreased the activity of AST, LDH and CK in serum of MSG treated rats. These results in agreement with the studies of **Hazar*et al.***[43]who reported that treatment with β carotene administered intraperitoneally three times a week for three weeks one hour before MSG injection markedly lowered

the serum values of lactate dehydrogenase, creatine phosphokinase and aspartate aminotransferase to values close to those of control rats.

Tesoriere*et al.*[44] observed that treatment of rats with vitamin A, once a day for 2 days, before injecting doxorubicin, substantially reduced the peroxidative damage to heart lipids and proteins, and markedly lowered the serum values of lactate dehydrogenase and creatine phosphokinase to values close to those of control rats.

Firdous and Kuttan[45]reported that oral administration of carotenoid was started 15 days prior to doxorubicin intraperitoneal single dose injection. Serum markers of cardiac injury LDH, CPK, SGOT and SGPT levels, which were increased drastically by doxorubicin treatment, were decreased to normal level by carotenoid treatment.

In the present results, treated rats with β carotene caused significantly increased myocardium reduced glutathione (GSH) level**,**superoxide dismutase (SOD) level and decrease malondialdehyde in cardiac tissues. These results in agreement with the studies of **Abdel Baky*et al.*[19]** whom reported that treatment with β carotene administered intraperitoneally three times a week for three weeks one hour before MSG injection markedly increased myocardium reduced glutathione (GSH) level, superoxide dismutase (SOD) level and decrease Malon-dialdehyde in cardiac tissues.

Previous studies reported that carotenoids are capable of scavenging free radicals and inhibiting lipid peroxidation[46,47]and pro-inflammatory mediators and inducing detoxifying enzymes[48]**.** β carotene was also reported for its anti-inflammatory and antioxidant potential actions[49]and has the ability to inhibit no production in several type of cells and attenuate oxidative tissue damage[50]**.**

The beneficial effect of β carotene administration on oxidative damage is related to its activity as a direct and potent free scavenger. First, β carotene enhances the levels of endogenous glutathione by increasing intracellular cysteine and subsequently potentiates the natural anti-oxidative cellular defense mechanism[51]**.**

In the present study, the results showed that treatment with curcumin significantly decreased the serum level of AST, LDH and CK in MSG treated rats. In agreement with the studies of **Agadihiremath*et al.*[52]** who observed that curcumin significantly protect myocardium from the toxic effects of MSG by reducing the elevated serum level of LDH, CPK and AST to the normal. Normalization of CK and LDH elevated levels and increasing percentage of survivors by *C. longa* L extracts confirms the cardio-protective effects of curcumin[53,54,55]**.** Curcumin is the main bioactive compound in these plant extracts, increases the cardiac glutathione content, suggesting that it may augment the action of these naturally occurring sulfhydryl groups to maintain membrane integrity with concomitant decrease of enzymes leakage from the cardiocytes, protection of cardiac tissue from damage, and improvement survival of rats[56]**.**

The present datashowed that treatment with curcumin significantly increased myocardium reduced glutathione (GSH) level, superoxide dismutase (SOD) level and decreased Malondialdehyde in cardiac tissues. The obtained results are in line with the results of**Zhong*et al.*[57]*,*** these observed that curcumin reduced the myocardial infarct sizes, the serum CK and LDH activity. The myocardial MDA declined while SOD and GSH-Px activity were increased markedly.

Also, **El-Sayed *et al.*[58]**observed that oral administration of *Curcuma longa ethanolic* or water extract prior to doxorubicin produced a significant protection which was evidenced by significant reduction in mortality, CK and LDH activities. Moreover, they significantly increased GSH, markedly decreased cardiac calcium and cardiac MDA.This may be due to its function of curcumin in inhibition of lipid peroxidation, augmentation of endogenous antioxidants and improving myocardial metabolism**.**

The oxidative cardiac tissue damage induced by toxic effect of MSG in rats was ensured by pronounced increase in the activities of diagnostic serum marker enzymes, CPK and AST compared to normal rats and confirmed by the histopathological picture which demonstrated focal myonecrosis. These findings confirm the onset of myocardial lesion and leaking out of the marker enzymes from heart to blood[38,39]**.**

Histopathological examination of the hearts of MSG injected rats showed that marked changes that were expressed as focal area of coagulative necrosis of the myocardium.The myofibers showed Karyopyknosis,

hypereosinophilia and loss of striation. Infiltration of macrophage in the interstitium and thrombosis of blood vessels can be also observed.These results are in agreement with **Paul *et al.*[59]** reported that chronic oral administrationof MSG (4g/kg body weight) to adult wistar rats for a period of 180days caused oxidative stress and histological alteration to the cardiac tissue, as cloudy swelling, fibers separationand vascular congestion.

Zaki[60]reported that, after one week MSG exposure induces morphological cardiac alterations and beta-carotene supplementation attenuates this ventricular remodeling process and most fibers showed normal morphological aspects

Histopathological findings of curcumin treated myocardial hearts showed a near normal morphology of cardiac muscle. They revealed only congestion of blood vessels with normal myofibres with the absence of necrosis compared to the hearts of MSG injected rats.The obtained results are in agreement with the results of **Abdel Baky*et al.*[19]**who reported that heart of MSG-injected animals showing areas of necrotic focal lesion. Heart of rats received β-carotene prior to MSG injection showing more or less normal muscle fibres. Heart of rats received currcumin prior to MSG injection showing normal muscle fibres.

Histopathological findings of the used antioxidants in the treated cardiomyopathy heart show a near normal morphology of cardiac muscle with the absence of necrosis compared to MSG-induced heart. The biochemical and histological results presented in the current investigation suggest the ability of the β-carotene and curcumin to protect and stabilize cellular membranes against monosodium glutamate cardio-toxicity.

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