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Vitamin E Suppresses Aortic Ultrastructural Alterations Induced by Toxic Doses of Monosodium Glutamate

La Vitamina E Suprime las Alteraciones Ultraestructurales Aórticas Inducidas por Dosis Tóxicas de Glutamato Monosódico

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SUMMARY: An association between certain food additives and chronic diseases is reported. Current study determined whether administering toxic doses of the food additive monosodium glutamate (MSG) into rats can induce aortopathy in association with the oxidative stress and inflammatory biomarkers upregulation and whether the effects of MSG overdose can be inhibited by vitamin E. MSG at a dose of (4 mg/kg; orally) that exceeds the average human daily consumption by 1000x was administered daily for 7 days to the rats in the model group. Whereas, rats treated with vitamin E were divided into two groups and given daily doses of MSG plus 100 mg/kg vitamin E or MSG plus 300 mg/kg vitamin E. On the eighth day, all rats were culled. Using light and electron microscopy examinations, a profound aortic injury in the model group was observed demonstrated by damaged endothelial layer, degenerated smooth muscle cells (SMC) with vacuoles and condensed nuclei, vacuolated cytoplasm, disrupted plasma membrane, interrupted internal elastic lamina, clumped chromatin, and damaged actin and myosin filaments. Vitamin E significantly protected aorta tissue and cells as well as inhibited MSG-induced tissue malondialdehyde (MDA), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). The highest used vitamin E dosage was more effective. Additionally, a significant correlation was observed between the aortic injury degree and tissue MDA, TNF-α, IL-6, and superoxide dismutase (SOD) levels (p=0.001). Vitamin E effectively protects against aortopathy induced by toxic doses of MSG in rats and inhibits oxidative stress and inflammation.

KEY WORDS: Monosodium glutamate; Aortic injury; Ultrastructural damage; Oxidative stress; Vitamin E; Animal model.

INTRODUCTION

Food additives such as sodium nitrite and monosodium glutamate (MSG) used in the food industry have been associated with potentially harmful effects such as allergic reactions, digestive disturbance, mood swing and depression, headaches and dizziness, kidney and liver diseases, and cancer (Eweka *et al*., 2011; Sharma, 2015; Zhang *et al*., 2019). It is estimated that in the United States of America, the average daily consumption of MSG per person is 0.2–0.5 g, and more than triple in Korea (He *et al*., 2011). Several animal works demonstrated the harmful effects of toxic dose MSG; for example, (i) MSG given to mice for seven days at doses of 4 and 8 mg/g was reported to lower cardiac tissue levels of antioxidants and increased oidative stress tissue levels (Singh & Ahluwalia, 2012); (ii) toxic doses of MSG induced in rats cardiac arrhythmia, oxidative kidney damage, and hepatocellular damage (Onyema *et al*., 2006; Liu *et al*., 2013; Wang *et al*., 2015) ; (iii) MSG induced obesity in rats that caused hepatic steatosis and a significant rise in liver injury biomarkers, AST and ALT, as well as TNF-α and IL-6 gene expression (Wang *et al*., 2015) ; (iv) oxxidative liver damage was induced in rats that received for a duration of 10 days low dose of MSG (0.6 mg/gram)(6); and (v) intraperitoneal injection of 4 mg/gram MSG into rats markedly increased liver, kidney, and

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brain biomarkers of oxidative stress and decreased antioxidants (Farombi & Onyema, 2006).

Vitamin E is a fat-soluble antioxidant and anti-inflammatory drug (Haidara *et al*., 2003; Rizvi *et al*., 2014; Ramanathan *et al*., 2018). It is reported to decrease arterial blood pressure(Tian *et al*., 2005), prevents atherosclerotic plaque formation in mice (Meydani *et al*., 2014), protects against ageing-induced cardiovascular disease via the inhibition of inflammation, abnormal lipid profile, and improving mitochondrial function (Ramanathan *et al*., 2018), as well as lowering coronary heart disease in humans (Spencer *et al*., 1999; Vardi *et al*., 2013). Furthermore, vitamin E is proposed to improve liver function in patients with non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD), liver fibrosis, and hepatocellular ballooning (Violi & Cangemi, 2010). However, neither the adverse effect of toxic doses of MSG on aortic tissue nor the potential protection against MSG overdose-induced aortopathy by vitamin E has been investigated before in an animal model. Therefore, this study proposed that very high doses of MSG can induce acute aortic injury and aortic ultrastructural damage in rats that could be ameliorated by vitamin E.

MATERIAL AND METHOD

Animals. Sprague-Dawley rats (170-200 g) were used, and all animal work was handled in accordance with King Khalid University guidelines for care and handling of animal work. Rats were kept in a clean facility, at a constant temperature of 22 °C, with a 12 hours light / dark cycle, and had free access to water and animal food.

Experimental design. Rats were divided into four groups (n = 6 per group), after a one-week acclimatization period: Control group (Control): non-treated rats; MSG group (MSG): for seven consecutive days, rats were given MSG (4 mg /kg, orally); MSG+Vit E100 group: rats were given MSG (4 mg /kg, orally) plus vitamin E (100 mg/kg, orally) for a period of 7 days; and MSG+Vit E300 group: rats were given for a period of 7 days MSG (4 mg /kg, orally) plus vitamin E (300 mg/kg, orally). Rats were then culled 24 h after the end of the treatment.

Analysis of aortic tissue levels of MDA, IL-6, superoxide dismutase (SOD), and TNF-α. As we previously reported (Dallak *et al*., 2019), aortic samples were obtained from all rats on the 8th day were washed with PBS and homogenized in cold PBS-EDTA, pH 7.4. The supernatant was collected and stored at -70 °C to determine the levels of MDA, IL-6, TNF-α, and SOD in the tissue. TNF-a ELISA kit (Cat No. ab46070) was obtained from Abcam, Cambridge, UK; IL-6 ELISA kit (Cat No. ELR-IL6-001) was purchased from RayBio, GA, USA; and Superoxide dismutase (SOD) assay kit (Cat. No.706002) was obtained from Cayman Chemical, Michigan, USA. Whereas, malondialdehyde (MDA, Cat No. NWK-MDA01) assay kit was obtained from NWLSS (Vancouver, BC, Canada). All materials were used as directed by the manufacturer.

Histological analysis. Prior to alcohol dehydration and embedding with paraffin, aorta specimens were collected and fixed for 24 h using the standard method (Al-Hashem *et al*., 2019). Using hematoxylin and eosin (H&E), aorta 5μm thick paraffin sections were stained, and then they were analyzed for structural changes.

Transmission Electron Microscopy (TEM). Aorta ($1mm^3$) per piece underwent fixation with 4 % glutaraldehyde at 4 ºC with 0.2 M cacodylate buffers and processing for TEM examination as previously described (Dallak *et al*., 2019).

Statistical and morphometric analysis. All data are expressed as mean ± standard deviation (SD). Statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test. Image analyzer (Leica Qwin 500 C, Cambridge, UK) was used for assessing the degree of aortic tissue damage in 10 high power fields/rat of H&E-stained sections. Quantitative data were arranged as a means and standard deviations (SD) and compared using ANOVA followed by post-Hoc analysis (Tukey test). Results were considered significant at a p-value ≤ 0.05.

RESULTS

MSG overdose induces acute aortopathy in rats. To determine whether toxic doses of MSG can induce aortic damage, the model group received MSG (4gm /kg, orally) daily for seven days and culled after 24 hours. Harvested aortas were prepared for tissue homogenates and transmission electron micrographs. Representative TEM image (10,000x) of aorta sections prepared from the SMC layer of the control group of rats displays normal ultrastructural architecture demonstrated by normal SMC surrounded by undamaged plasma membranes with a single nucleus, actin and myosin filaments forming lattice-like networks (asterisks), and few mitochondria (Fig. 1A). TEM image at a similar magnification that represents tunica media of the aorta sections of the model group displays mild extracellular edema, disruption of elastin

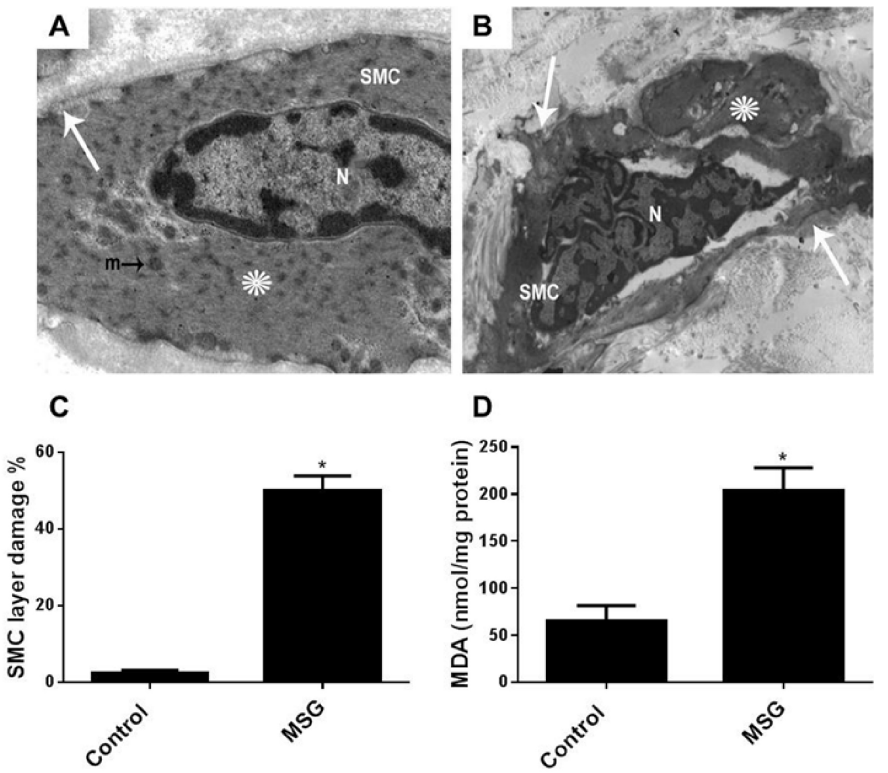

Fig. 1. MSG induces acute aorta injury. Using transmission electron microscopy, images (8,000x) of the tunica intima layer from the aorta of the MSG group of rats (B) are compared with the control group (A). The plasma membrane is indicated by arrowheads, while the intimal surface is indicated by white arrows. Abbreviations: N, nucleus; En, endothelial cell; L, lipid droplet; V, vacuole; Lu, tubular lumen; SMC, smooth muscle cell. (C). Semi-quantitative analysis of the degree of tunica intima damage induced by high doses of MSG compared with the control rats was measured in the MSG group compared to the control group of rats. Results represent the mean (±SD). *p<0.05 versus control. Aortic tissue levels of MDA (D) were measured in the MSG and control animal groups. Results represent the mean (±SD); n=6 for each group. *p<0.05 versus control. MSG: monosodium glutamate; MSG: monosodium glutamate; TEM: transmission electron microscopy; MDA: malondialdehyde.

fibers,apoptotic SMC enclosed by irregular-shaped plasma membranes showing a damaged lattice-like network of actin and myosin, and pyknotic nuclei with clumped chromatin (Fig. 1B). In addition, histograms that represent the quantitative analysis of SMC layer damage demonstrated significant destruction (50.0±3.9 % in MSG treated versus 2.3±0.8 % in control animals) of the layer by MSG ($p<0.0001$), as shown in Figure 1C. Furthermore, significant aortic tissue levels of the oxidative stress biomarker MDA in the MSG group were also observed ($p<0.0001$) (208.1±23.3 nmol/mg in MSG treated versus 64.5±17.0 nmol/mg in control animals), as found in Figure 1D.

Vitamin E protects against MSG overdose-induced aortic tissue biomarkers of oxidative stress and inflammation. A link between oxidative stress and inflammation and aortopathy is documented. Therefore, MDA, SOD, IL-6, and TNF-α were measured in aortic tissue homogenates of all four animal groups (Fig. 2) in order to assess the inhibition level of oxidative stress and inflammation biomarkers by two vitamin E different doses. In comparison to the untreated control group's normal values for these parameters, MSG toxic doses caused a three-fold increase in MDA (208.1±23.3 nmol/mg in MSG treated versus 64.5±17.0 nmol/mg in control animals) (Fig. 2A) and > two-fold decrease in the antioxidant SOD (1.5±0.6 U/mg in MSG treated versus 4.2±0.4 U/mg in control animals) (Fig. 2B). MSG also augmented IL-6 by four-fold (125.8±9.9 pg/mg in MSG treated versus 29.7±5.5 pg/mg in control animals) (Fig. 2C) and TNF-α by three-fold (121.3±16.1 pg/mg in MSG treated versus 32.5±4.3 pg/mg in control animals) (Fig. 2D). All these parameters were significantly protected by vitamin E (85.3±11.9, 3.5±0.5, 52.7±10.6, 65.8±12.7in MDA, SOD, IL-6, and TNF-α respectively). The relative degree of inhibition of MDA and IL-6 by vitamin E was Vit E300 >Vit E100 (85.3±11.9 in Vit E300 versus 109.7±5.8 in Vit E100 and 52.7±10.6 in Vit E300 versus 71.2±11.6 in Vit E100 for MDA and IL-6 respectively).

Vitamin E protection against MSG-induced aortopathy overdose. To find if vitamin E can offer protection to the aorta architecture against potential injury caused by MSG toxic doses, the effect of two vitamin E doses (100 and 300 mg/kg) were evaluated and given simultaneously with MSG to two groups of treated rats for seven days. Aorta tissues were harvested and stained with H&E for examination under light microscopy. The control group showed a normal histological structure of aortic tissues (Fig. 3A), as demonstrated by the normal endothelial layer, elastic lamina, and smooth cells. H&E image represents aortic sections from the MSG group of rats (Fig. 3B), which shows disorganized tissue architecture, damaged endothelial layer, degenerated smooth muscle cells (SMC)

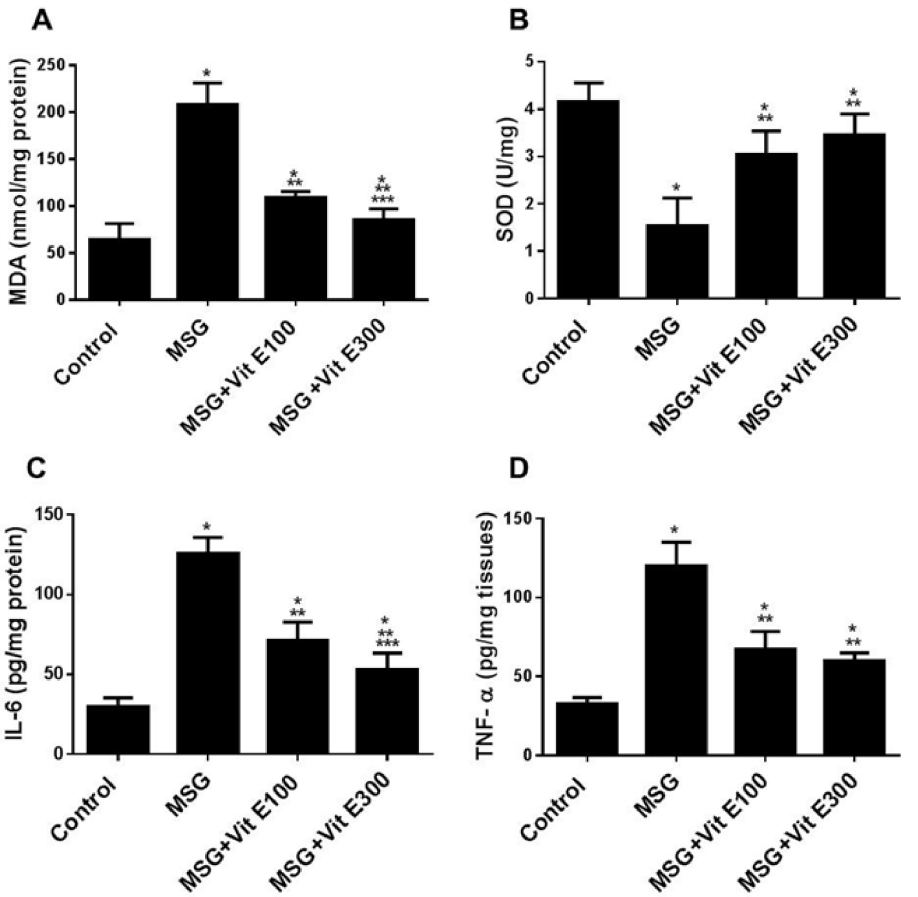

Fig. 2. Vitamin E inhibits oxidative stress and inflammation biomarkers that are MSG-induced. In four rat groups, MDA (A), SOD (B), IL-6 (C), and TNF-α (D) levels in aorta tissue were determined. Results represent the mean (±SD); n=6 for each group. *p<0.05 versus control, **p<0.05 versus MSG, ***p<0.05 versus MSG+Vit E100.MSG: monosodium glutamate; SOD: superoxide dismutase; MDA: malondialdehyde; Vit E: vitamin E; IL-6: interleukin-6; TNF-α: tumor necrosis factor-alpha.

with vacuoles, pyknotic nuclei, and abnormal elastic lamina. A dose of 100 mg/kg of vitamin E reduced the MSG toxic effect on the aorta (Fig. 3C). However, some abnormal SMC with vacuoles can still be seen. On the other hand, in comparison to the control group, the normal aortastructure was maintained by giving 300 mg/kg vitamin E (Fig. 3D). Furthermore, quantification of endothelial and SMC damage demonstrated a significant ($P < 0.0001$) destruction of these layers by MSG (59.2±5.6 %, 48.8±5.5 % in MSG treated versus 0.4±0.2 % and 0.4±0.2 % for endothelial and SMC layers respectively) and effective ($P < 0.0001$) inhibition by vitamin E (7.2±0.8 % and 3.5±0.5 % for endothelial and SMC layers respectively) (Figs. 3E and 3F).

Vitamin E protection against MSG overdose induced aortic ultrastructural alterations. In light of the above-mentioned findings that vitamin E significantly inhibited oxidative stress and inflammatory markers and substantially protected the histology of aortic tissue in the treated groups of rats, we then investigated whether vitamin E can also protect the aorta ultrastructure from MSG toxic dose induced changes. TEM images of aorta prepared from the control rats displayed normal architecture of the tunica intima (Fig. 4A) compared to profound damage in TEM prepared tissue that represents aorta sections of MSG-treated rats (Fig. 4B). Vitamin E administration to the rats model group (100 mg/kg; MSG+VitE100) (Fig. 4C) provided partial protection to the aortic endothelial layer architecture as demonstrated by cytoplasmic vacuoles, condensation of chromatin material, and still damaged plasma membrane. Whereas 300 mg/kg vitamin E provided better protection to the endothelial layer ultrastructure since a representative TEM image prepared from this group displays intact endothelial cell structures (Fig. 4D). We further determined the correlation between the score of aortic endothelial layer ultrastructural alterations and the tissue levels of MDA and IL-6 in order to provide additional support for an association between aortopathy and oxidative stress and inflammation in addition to confirming the stability and approperiatness of vitamin E in aortopathy induced by MSG intoxication. A positive correlation was detected between endothelial layer injury (%) and these parameters; the oxidative stress biomarker MDA (nmol/mg)($r = 0.957$; $P < 0.0001$) (Fig. 4E) and the inflammatory biomarker IL-6 (pg/mg) ($r = 0.907$; $P < 0.0001$) in all rats' groups (number of XY pairs = 24) after the completion of the experiment (Fig. 4F).

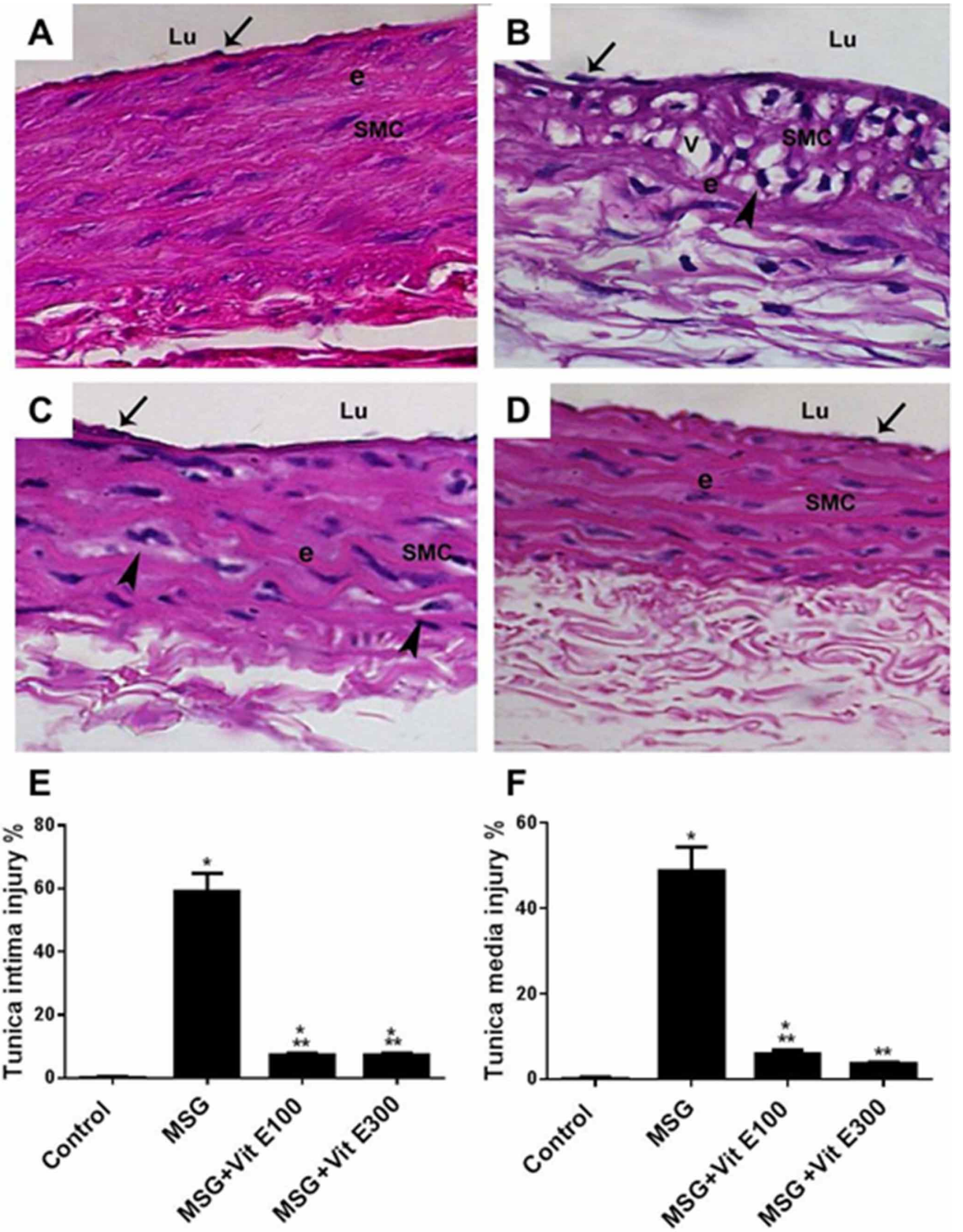

Fig. 3. Vitamin E protects the aorta architecture from MSG-induced damage. H&E stained sections (400x) of the aorta from the control (A), MSG (B), MSG+Vit E100 (C), and MSG+ Vit E300 (D) groups. Arrows in (A-D) point to the endothelial layers, and arrowheads in (B and C) point to the small condensed nuclei and damaged area in the SMC layer, respectively. Abbreviations: Lu, lumen; e, elastic lamina; SMC, smooth muscle cells; and V, vacuoles. (E and F) Semi-quantitative analysis of the degree of tunica intima (endothelial layer) and tunica media (MC layer) damage, respectively, induced by MSG compared with the vitamin E treatments and control rats. *p<0.05 versus control, **p<0.05 versus MSG, ***p<0.05 versus MSG+Vit E100. MSG: monosodium glutamate; H&E: hematoxylin and eosin; Vit E: vitamin E.

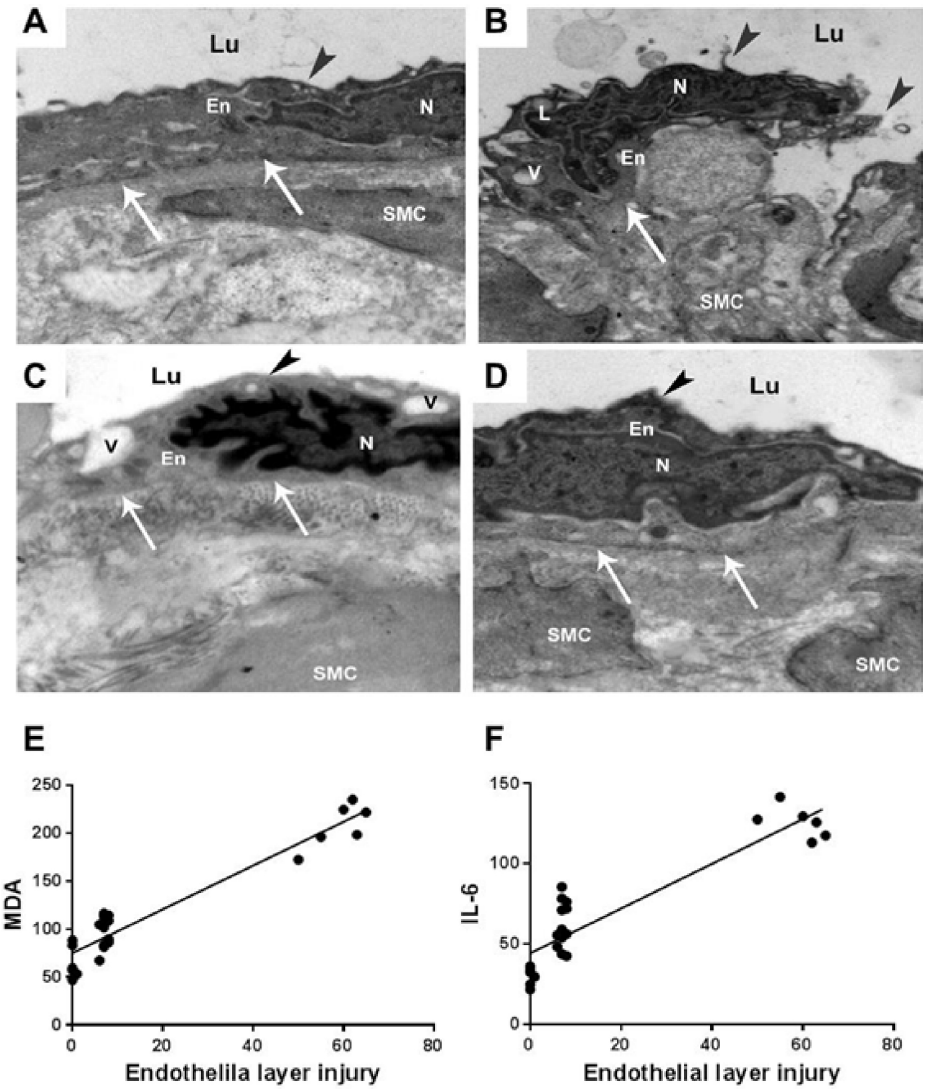

Fig. 4. Vitamin E protects against the ultrastructural changes caused by MSG in the aortic endothelial layer.TEM images (8000x) of the aortic endothelial layer from the control (A), MSG (B), MSG+Vit E100 (C), and MSG+Vit E300 (D) groups. Arrowheads point to the plasma membrane, and white arrows point to the intimal surface. Abbreviations: N, nucleus; En, endothelial cell; L, lipid droplet; V, vacuole; Lu, tubular lumen; SMC, smooth muscle cell. Correlation between the scoring of endothelial layer damage and MDA and IL-6. The degree of aortic endothelial ultrastructural alterations was evaluated in all rats, and its correlation with MDA and IL-6 is shown (E and F). MSG: monosodium glutamate; TEM: transmission electron microscopy; Vit E: vitamin E; MDA: malondialdehyde; IL-6: interleukin-6.

TEM images that assess the SMC layer (tunica media) ultrastructural alterations induced by MSG in comparison to the control untreated and vitamin E treated animal groups are depicted (Fig. 5). Representative TEM image (10,000x) of aorta sections from the SMC layer of the control group of rats displays normal ultrastructural architecture as demonstrated by SMCs in their normal state surrounded by intact plasma membranes and containing a single nucleus, actin and myosin filaments in lattice-like networks, and a few mitochondria(Fig. 5A). TEM image at a similar magnification that represents tunica media of the aorta sections of the model group displays mild extracellular edema, disruption of elastin fibers, apoptotic SMC enclosed by irregular-shaped plasma membranes showing damaged myosin and actin of the lattice-like network, and pyknotic nuclei with clumped chromatin (Fig. 5B). Treating the MSG group of rats with vitamin E (100 mg/kg; MSG+VitE100) (Fig. 5C) provided substantial protection to the SMC layer architecture that was

demonstrated by almost normal cells with a single nucleus, a rough endoplasmic reticulum, a few mitochondria, and lattice-like networks of myosin and actin filaments enclosed by undamaged plasma membranes. However, vacuolated cytoplasm can be seen, which means partial protection. Better protection to the tunica media ultrastructure was obtained with 300 mg/kg vitamin E (Fig. 5D). Furthermore, the correlation between the score of SMC layer ultrastructural alterations and the tissue levels of TNF-α and SOD was determined to provide additional endorsement for linking aortic injury with oxidative stress and inflammation. As shown in Fig.5E, a positive correlation was found between the SMC layer injury % and the inflammatory biomarker TNF-α (pg/mg) ($r = 0.904$; $P < 0.0001$). In contrast, a negative correlation was found between the SMC layer injury % and the antioxidant SOD (U/mg) ($r = -0.837$; $P < 0.0001$)in all rats' groups (number of XY pairs = 24) after the completion of the experiments shown in Figure 5F.

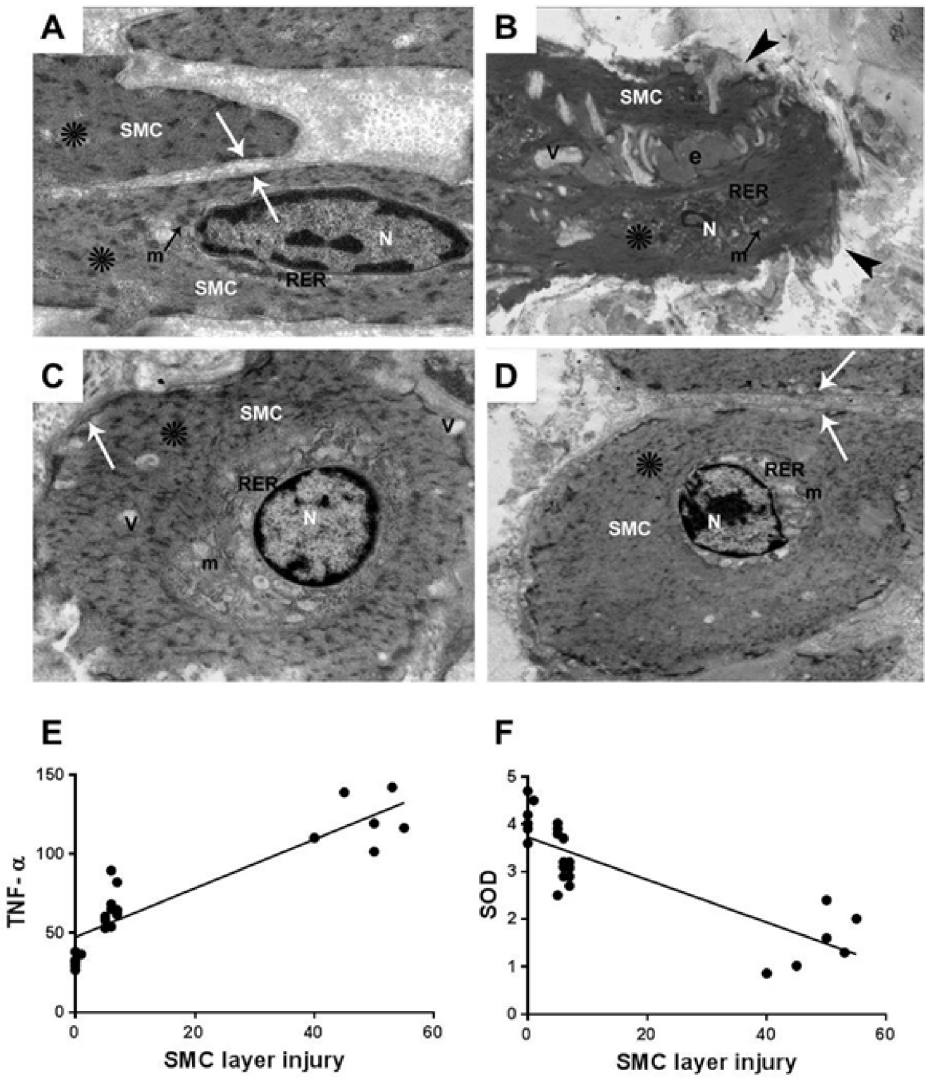

Fig. 5. Vitamin E protects aortic SMC layer ultrastructural alterations in rats induced by MSG. TEM images (10000x) of the aortic endothelial layer were obtained on the 8th day from the control (A), MSG (B), MSG+Vit E100 (C), and MSG+Vit E300 (D) groups. The damaged plasma membrane is indicated by arrowheads, the lattice-like networks of actin and myosin filaments are indicated by asterisks, and the intact plasma membranes are indicated by white arrows. Abbreviations: N, nucleus; m, mitochondria; RER, rough endoplasmic reticulum; e, elastic fiber; SMC, smooth muscle cell; V, vacuole. Correlation between the scoring of SMC layer damage and TNF-α and SOD. The degree of aortic SMC ultrastructural alterations was evaluated in all rats, and its correlation with TNF-α and SOD are shown (E and F). MSG: monosodium glutamate; TEM: transmission electron microscopy; Vit E: vitamin E; SOD: superoxide dismutase; TNF-α: tumor necrosis factor-alpha.

DISCUSSION

The principal findings in this study were that (i) toxic doses of MSG exceeding the human consumption by about 1000x induced acute aortopathy and alterations to aortic layers ultrastructure in rats in association with the inflammation and oxidative stress biomarkers induction. (ii) the antioxidant and anti-inflammatory drug vitamin E was able to inhibit the deleterious effects of MSG; (iii) aortic injury and inflammation and oxidative stress were significantly correlated. These conclusions are reinforced by the results showing that MSG induced intense injury affecting aorta architecture (Fig. 3) and aorta layers, tunica intima and tunica media ultrastructure (Figs. 4 and 5), and augmented the tissue levels of oxidative stress and inflammation (Fig. 2) that were significantly protected by vitamin E (Figs. 2 to 5). Also, the present results that reveal a significant correlation between the aortic endothelial score and SMC layers damage and MDA, IL-6, TNF-?, and SOD (Figs. 4 and 5) support our conclusion mentioned above. However, tissue injuries were more efficiently protected by the highest used vitamin E dosage (Figs. 3 to 5). Whereas both vitamin E doses (100 and 300 mg/kg) inhibited inflammation and oxidative stress biomarkers (Fig. 2). Thus, the present findings supported our working hypothesis that toxic dose of MSG can cause aortic tissue injury and ultrastructural damage and that vitamin E has a protective role against MSG overdose-induced acute aortopathy in rats.

The current data that point to MSG toxic dose-caused aortopathy is in line with a previous report that demonstrated the induction of bradycardia and tachyarrhythmias in normal and myocardial infarcted rats, respectively by MSG (Liu *et al*., 2013). In addition, previously published work that showed MSG overdose-induced liver damage in rats and chicken embryos (Elbassuoni *et al*., 2018) and kidney injury and renal ultrastructural damage (Elbassuoni *et al*., 2018; Eid *et al*., 2019a) in rats are also in agreement with this work that points to the damaging effects of MSG overdose on the aorta. Furthermore, our data that point to MSG-induced inflammation and oxidative stress associated with aortopathy support previous findings of MSG increased oxidative stress of cardiac tissue (Hazzaa *et al*., 2020) and kidney infiltration of inflammatory cells (Contini *et al*., 2017).

Finally, the present data suggesting that vitamin E protects adequately against acute aortic injury caused by 4 g/kg MSG for a period of eight days are in line with our recent work that demonstrated effective protection to the hepatocyte ultrastructural alterations induced by the same toxic dose of MSG (Eid *et al*., 2019b) and also in agreement with a previous report that showed that vitamin E inhibited acute and chronic kidney injury induced by giving 4 g/kg MSG to rats over one week and 6 months, respectively (Paul *et al*., 2012; Eid *et al*., 2019a,b).

In summary, these findings demonstrate that administering very high doses of MSG for a period of 7 days in rats caused ultrastructural alterations in both aortic tunica intima and tunica media layers as well as acute aortic injury in addition to augmenting inflammation and oxidative stress and that the fat-soluble antioxidant and anti-inflammatory drug, vitamin E effectively protects against these changes in rats. We also show(i) that vitamin E at 300 mg/kg is more effective in most investigations than 100 mg/kg vitamin E; and (ii) an association between aortic tissue damage and inflammation and oxidative stress markers is observed.

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RESUMEN: Se reporta una asociación entre ciertos aditivos alimentarios y enfermedades crónicas. El objetivo de este estudio fue determinar si la administración de dosis tóxicas del aditivo alimentario glutamato monosódico (MSG) en ratas puede inducir aortopatía en asociación con el estrés oxidativo y la regulación positiva de los biomarcadores inflamatorios y si el efecto de una sobredosis de MSG se puede inhibir con vitamina E. Se administró MSG diariamente durante 7 días una dosis de (4 g/kg; por vía oral) que excede el consumo diario humano promedio, en 1000x a las ratas del grupo modelo. Mientras que las ratas tratadas con vitamina E se dividieron en dos grupos y se administraron dosis diarias de MSG más 100 mg/kg de vitamina E o MSG más 300 mg/kg de vitamina E. Todas las ratas fueron sacrificadas en el octavo día. Usando exámenes de microscopía óptica y electrónica, se observó una lesión aórtica profunda en el grupo modelo demostrada por

una capa endotelial dañada, células musculares lisas degeneradas (SMC) con vacuolas y núcleos condensados, citoplasma vacuolado, membrana plasmática rota, lámina elástica interna interrumpida, cromatina agrupada y filamentos de actina y miosina dañados. La vitamina E protegió significativamente el tejido y las células de la aorta, además de inhibir el malondialdehído tisular (MDA) inducido por MSG, la interleucina-6 (IL-6) y el factor de necrosis tumoral alfa (TNF-α). La dosis más alta de vitamina E utilizada fue más efectiva. Además, se observó una correlación significativa entre el grado de lesión aórtica y los niveles tisulares de MDA, TNF-α, IL-6 y superóxido dismutasa (SOD) (p=0,001). La vitamina E efectivamente protege contra la aortopatía inducida por dosis tóxicas de MSG en ratas e inhibe el estrés oxidativo y la inflamación.

PALABRAS CLAVE: Glutamato monosódico; Lesión aórtica; Daño ultraestructural; Estrés oxidativo; Vitamina E; Modelo animal.

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