ORIGINAL ARTICLE

A-Tocopherol protects against monosodium glutamate-induced hepatotoxicity via modulation of liver enzymes and collagen deposition in adult Wistar rats

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ABSTRACT

Monosodium glutamate (MSG) is a flavor enhancing agent known for its potential adverse effects, particularly its toxicity to the liver through the induction of oxidative stress. The current study evaluated the protective potential of α-tocopherol on MSG-induced hepatotoxicity in adult Wistar rats. In this experiment, adult Wistar rats, 20 in number, each weighing between 160g and 170g, were systematically allocated into four groups made up of five rats per group: Group A (control group), Group B (administered 200 mg/kg body weight [BW] of MSG), Group C (received 100 IU/kg BW of vitamin E one hour prior to the MSG treatment), and Group D (given 100 IU/kg BW of vitamin E only). After administration, the rats were sacrificed, and liver function, oxidative stress markers, and histology were assessed. Results showed that MSG significantly increased ALT, AST, albumin, and total bilirubin levels, indicating altered liver enzyme activity. MSG also induced oxidative stress, evidenced by significantly decline [$p<0.05$] levels of antioxidant enzymes (superoxide dismutase, catalase and glutathione peroxidase) along with a significant elevation in malondialdehyde as well as zonal necrosis and mild Kupffer cell activation, with increased collagen deposit in the liver. However, treatment with α-tocopherol significantly improved liver enzyme biomarkers, increased antioxidant enzyme activity and reduced lipid peroxidation as well as marked improvements in liver histology as evidenced by relatively normal liver histoarchitecture and reduced deposits of collagen fibers. Evidences from this study suggest that α-tocopherol confers protective effects on MSG-induced hepatotoxicity by modulating oxidative stress, liver enzymes and collagen deposition, elaborating its potency as a therapeutic agent against hepatotoxicity.

Keywords: Hepatotoxicity, Monosodium glutamate, Liver, Vitamin E, α-Tocopherol

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INTRODUCTION

The increase in processed food consumption has become more noticeable in recent years due to changes in lifestyle and eating habits. Many of these processed foods contain high levels of flavor enhancers, with MSG being one of the most common. MSG is marketed under various brand names, including, Sasa, Ajinomoto, Miwon Vetsin and Weichaun [3]. While MSG is popular and commonly used in cooking around the world, its safety remains a topic of ongoing debate. Several studies have linked excessive intake of MSG to various health conditions and disorders. MSG poses a significant risk due to its ability to overstimulate glutamate receptors in the brain, which can lead to excitotoxicity and potential damage to liver cells. Furthermore, some research has suggested that consuming MSG may be associated with the onset of non-alcoholic fatty liver disease (NAFLD), a condition characterized by fat buildup in the liver [1,5].

The widespread use of MSG in processed foods, restaurant dishes, and fast food has resulted in significant exposure levels among populations worldwide, as highlighted by epidemiological studies [6]. Consequently, there are growing concerns regarding the chronic consumption of MSG and its potential long-term deleterious consequences on liver. The liver is a vital organ responsible for metabolizing and detoxifying substances consumed by the body [7], including MSG. When MSG is consumed in large amounts, it may exceed the liver's ability to effectively detoxify it, potentially resulting in oxidative stress, inflammation, and damage to liver tissue [8,9]. Previous studies have demonstrated the hepatotoxic effects of MSG in animal models [8,9,10], thus, highlighting the need for interventions to mitigate these effects.

Vitamin E, a powerful antioxidant, helps protect cells from oxidative damage. It consists of a group of related compounds, primarily tocopherols and tocotrienols, which work by neutralizing free radicals and preventing lipid oxidation within cell membranes [11,12]. Due to its ability to neutralize free radicals and minimize lipid peroxidation, Vitamin E presents a promising option for protecting against MSG-induced liver damage. Therefore, this study investigated the protective potentials of α-tocopherol on MSG-induced liver damage in adult Wistar rats by exploring the impact of α-tocopherol on MSG-induced changes in oxidative stress markers, liver enzymes, collagen deposition, and the histomorphology of liver tissues.

MATERIALS AND METHODS

Chemicals and reagents

MSG used was purchased from Central Drug House [P] Ltd. Corp. Office: 7/28 Vardaan House, Daryaganj, New Delhi- 110002 [INDIA], with product code-037106. Vitamin E was purchased from Vixa Pharmaceutical Co. LTD. Ogudu, Lagos, Nigeria.

Experimental Design

Twenty adult Wistar rats were used for this study. Their weight ranges between 160.0 and 170.0 g. The animals were randomly grouped into four with five rats per group.

- Group A rats was the control group given 1 ml of water.
- Group B received 200 mg/Kg BW of MSG daily.
- Group C received 100 IU/Kg BW of Vitamin E an hour prior to 200 mg/Kg BW of MSG.
- Group D rats were given 100 IU/Kg BW of Vitamin E daily.

The treatment lasted for twenty-eight days, with all substances administered orally. The dosage of monosodium glutamate was based on the findings by Ogunlabi *et al.* [13] while the dose of Vitamin E was as determined by El-Hammady *et al*. [14]. The experimental protocols strictly followed the established guidelines by the Research Ethics Committee, College of Medical Sciences, University of Benin (CMS/REC/2024/357).

Evaluation of Body and Liver Weights

After 28 days, the body weights of the animals were assessed using an electronic balance. Following this, the rats were euthanized with chloroform anesthesia. Once sacrificed, their livers were carefully removed, blotted to eliminate any residual blood, and immediately weighed. Weights were documented. For each rat, weight change was calculated as the difference between the initial and final body weights. The hepatosomatic index was determined as the percentage ratio of hepatic weight to final body weight [15].

Assessment of Liver Function

This was done using blood samples that were centrifuged at 3,000 revolutions per minute for 10 minutes in order to separate the serum. The levels of serum ALT, AST and total bilirubin were assessed using Randox diagnostic kits [16], employing the colorimetric method. The bromocresol green (BCG) method [17] was used to analyze total serum albumin.

Oxidative Stress Parameters

The liver tissues were rinsed twice with cold phosphate-buffered saline (PBS). They were then homogenized and centrifuged and the supernatant collected. This was then used for analysis of endogenous antioxidant enzyme activities following standard protocols; SOD [18], CAT [19], GPx [20], and MDA [21].

Histological Assessment

The excised liver tissues were immediately fixed in 10% buffered formol-saline. They were subsequently processed and stained using haematoxylin and eosin [22] as well as Masson's trichrome [23]. The processed histological slides were assessed under a trinocular microscope equipped with a digital microscope camera.

Data analysis: The data acquired from this study was analyzed utilizing IBM statistical Package for Social Sciences, Version 23. Results were presented as [mean ± SEM]. Comparisons between groups were done utilizing analyses of variance [ANOVA]. *Post hoc* analysis was done using Tukey's Highest Square Difference [HSD]. Confidence level was set at 95% (P < 005).

RESULTS

Effect of treatment on weight: The control and Vitamin E-treated groups gained weight significantly [$p<0.05$], while there were no significant weight gains [$p>0.05$] in MSG-only and MSG + Vitamin E groups [figure 1A]. Weight gain was significantly lower MSG-treated group compared to the control [$p<0.05$]. However, MSG-treated group and MSG+Vitamin E-treated group had no significant difference [p>0.05] in weight gain [figure 1B]. There was significant declined [p<0.05] in hepatic weight in the MSG-treated group in comparison to the control. However, liver weight was significantly elevated [$p>0.05$] in MSG + Vitamin E group compared to MSG-treated group [figure 1C]. No significant differences were recorded in the hepatosomatic index across all groups [figure 1D].

Effect of treatment on liver function: Table 1 shows the effect of treatment on liver function. In comparison with the control, there were significant elevations [$p<0.05$] in ALT, AST, albumin, total bilirubin and total protein in the MSG-treated group. However, α-tocopherol significantly suppressed [$p<0.05$] ALT, AST, albumin, total bilirubin and total protein in comparison to the MSG-treated group.

Effect of treatment on oxidative stress: Table 2 shows the effect of treatment on antioxidant enzymes and lipid peroxidation across the experimental groups. In comparison to the control, GPx, SOD and CAT activities were significantly declined [$p<0.05$] while MDA level was significantly elevated [$p<0.05$] in the MSG-treated group. However, α-tocopherol significantly elevated the antioxidant enzyme activities [$p<0.05$] and while significantly suppressing [p<0.05] MDA level in comparison to the MSG-treated group.

Effect of treatment on liver histology: Photomicrographs of liver of the control group displayed normal histological features,

with radiating hepatocytes containing large round nuclei, well-defined sinusoids, and structures such as the portal vein and bile duct [Figure 2A], along with fine collagen deposits around the portal tract [Figure 3A]. Photomicrographs of the liver of MSG-only group exhibited zonal necrosis and mild activation of Kupffer cells [Figure 2B], and a dense distribution of collagen fibers around the portal tract [Figure 3B] which is evidence of severe fibrosis. However, co-administration with vitamin E displayed histoarchitecture similar to the control group [Figure 2C], and mild collagen deposition around the portal tract [Figure 3C]. Finally, photomicrographs of the liver of vitamin E-treated group showed normal histological features [Figure 2D] as well as mild collagen deposition around the portal tract was also mild [Figure 3D].

DISCUSSION

MSG's safety remains contentious due to its potential links to various health problems [24]. Given the widespread use of MSG, there are growing concerns about its long-term effects on liver health, as indicated by epidemiological studies [1,25]. Thus, this study assessed the hepatoprotective potential of α-tocopherol on MSG-induced liver damage in adult Wistar rats.

As weight fluctuations can indicate underlying health problems [26], they are necessary for assessment of the effects of chemicals and drugs. Morphological changes have been observed in the body and hepatic weights of MSG-treated rats, including weight loss [27] and reduced liver weight [28]. In this study, there was a remarkable decline in body weight changes and liver weight in rats treated with MSG. MSG has been reported to suppress appetite, impair nutrient absorption, and increase energy expenditure [29]. Also, MSG has been reported to potentially disrupt protein synthesis pathways or cause cellular atrophy [shrinkage] within the liver [28].

Liver enzymes are crucial for sustaining overall health, as they engage in numerous metabolic processes vital for the body's proper functioning. The levels of these enzymes serve as key indicators of liver health and function [30]. MSG has been associated with liver damage by causing elevations in key liver enzymes. Specifically, it impacts liver biomarkers which are essential for amino acid metabolism in liver cells [31]. Exposure to MSG leads to the release of liver enzymes into the bloodstream, resulting in elevated levels of these enzymes [32]. Furthermore, MSG exposure has been reported to disrupt the ability of the liver to breakdown bilirubin [33]. This disruption leads to a buildup of bilirubin in the blood [hyperbilirubinemia], potentially causing jaundice. In this study, MSG significantly increased ALT, AST, albumin and total bilirubin levels. This corroborates previous reports that MSG alters liver enzyme biomarkers [31,34]. However, on co-administration of MSG and vitamin E, there was a significant decrease in these biomarkers.

One of the key mechanisms proposed in MSG-induced liver toxicity is oxidative stress [35,36]. MSG stimulates oxidative stress by promoting free radical production. This usually develops following an imbalance between reactive oxygen species (ROS) formation and antioxidant defense system of the body, which suppresses the neutralizing potency of the cells. This imbalance can result from either increased ROS production, decreased defense mechanisms, or a combination of both. Results from this study showed that MSG significantly decreased antioxidant enzyme [SOD, CAT, and GPx] activity and caused an upsurge in lipid peroxidation [MDA]. This finding supports previous reports that MSG induces oxidative stress by suppressing the antioxidant enzyme activity and resultant elevation of lipid peroxidation in the liver tissues of experimental animals [35,36]. However, on co-administration of MSG and vitamin E, a significant elevation in antioxidant enzyme [SOD, CAT and GPx] activity, and a significant decline in MDA concentration were noted. This improvement in the

antioxidant defense system can be attributable to the antioxidant potentials of α-tocopherol.

The crucial role of liver histology in understanding the pathogenesis and progression of various liver diseases, including those induced by dietary factors such as MSG consumption cannot be overemphasized. In this study, the liver of rats treated with MSG-only showed zonal necrosis and mild Kupffer cell activation. This suggests that MSG causes significant damage to the liver. Zonal necrosis refers to the death of liver cells in specific zones within the liver lobule leading to disruption in the liver's ability to perform its vital functions [37,38,39]. Kupffer cells are liver macrophages responsible for removing debris and pathogens [28,40]. Their activation suggests an ongoing inflammatory response to MSG exposure [41,42]. These findings agrees with other studies elaborating that MSG induces hepatotoxicity in animal models [1,43,44]. Interestingly, the combined administration of monosodium glutamate (MSG) and α-tocopherol led to significant attenuation in liver histology. These findings are in agreement with others highlighting the antioxidant and hepatoprotective properties of α-tocopherol [45,46].

Liver fibrosis is a prevalent medical condition that can advance to cirrhosis and liver failure if not treated [47]. Oxidative stress and inflammation are common responses to tissue injury, and MSG has been linked to liver damage and fibrosis through its ability to trigger these processes [43]. Chronic liver damage can activate hepatic stellate cells, which are crucial in liver fibrosis by producing collagen and other extracellular matrix components [48]. This excessive deposition of collagen can lead to the formation of scar tissue, which can impair the normal function of the liver [49]. Findings from this study showed that the presence of densely distributed collagen fibres around the portal tract, in the liver tissue of MSG-treated rats. This suggests that MSG exposure led to liver damage and fibrosis, which is consistent with previous studies linking MSG consumption to liver injury [42,43]. However, the co-administration of MSG and vitamin E showed marked improvements as evidenced by the presence of mild collagen depositions around the portal tract. A-tocopherol, a commonly known antioxidant, may help minimize oxidative stress and inflammation linked to liver injury [45,50].

CONCLUSION

Evidences from this study suggest that α-tocopherol confers protective effects on MSG-induced hepatotoxicity by modulating oxidative stress, liver enzymes and collagen deposition, demonstrating its potency as a therapeutic agent against hepatotoxicity. Future studies should explore the underlying possible molecular mechanisms of these protective effects and assess their clinical relevance in humans.

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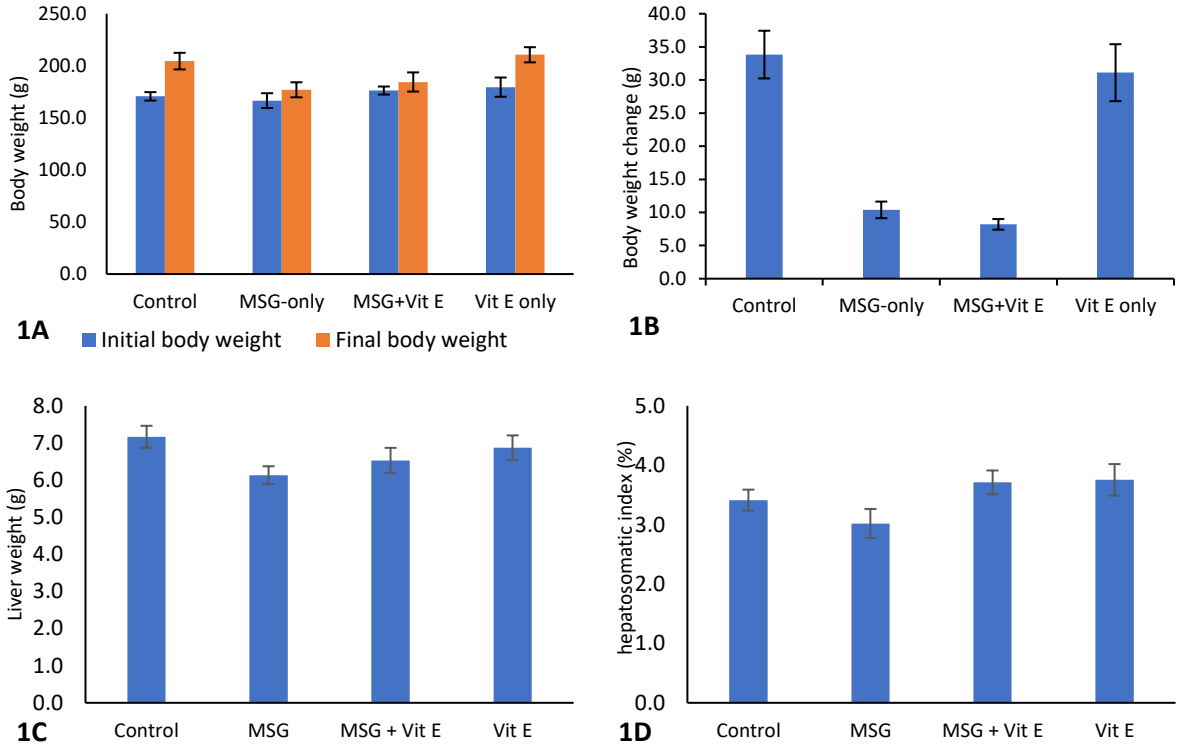

*Figure 1: Bar charts showing initial and final body weights (**1A:** upper left), body weight changes (**1B**: upper right), liver weight (**1C:** lower left) and hepatosomatic indices (**1D:** lower right) of the experimental animals. ^ means statistically significant difference between initial and final body weight in each group (P<0.05). *means statistically significant difference compared to control (P<0.05); # means statistically significant difference compared to MSG group (P<0.05).*

Table 1: effects of treatments on liver function in the experimental animals.

	Control	MSG	MSG+Vit. E	Vit. E	p-value
ALT (IU/L)	0.30±0.03	0.70±0.07*	0.42±0.02#	0.30±0.07	0.023
AST (IU/L)	0.60±0.06	1.25±0.12*	0.70±0.03#	0.51±0.02	0.041
Albumin (g/dL)	12.79±0.35	20.28±0.42*	13.97±0.42#	13.13±0.37	0.010
Total Bilirubin (µmol/L)	18.59±0.65	33.69±0.60*	20.18±0.56#	19.18±0.54	0.033

*Values are given as mean ±SEM. * p<0.05 (significantly different) compared with the control group; # p<0.05 (significantly different) compared to the MSG-only group.*

Table 2: effect of treatments on oxidative stress markers across the experimental groups.

	CONTROL	**MSG**	**MSG+VIT. E**	**VIT. E**	**p-value**
SOD (U/mg)	97.48±0.02	90.38±0.31*	95.89±0.31#	97.03±0.11	0.025
CAT (U/mg)	0.05±0.01	0.03±0.01*	0.04±0.01#	0.05±0.01	0.043
GPx (U/mg)	0.13±0.01	0.03±0.01*	0.10±0.01#	0.12±0.01	0.009
MDA (moles/mg)	0.80±0.04	2.65±0.11*	0.97±0.03#	0.87±0.11	0.004

*Values are given as mean ±SEM. * p<0.05 (significantly different) compared with the control group; # p<0.05 (significantly different) compared to the MSG-only group.*

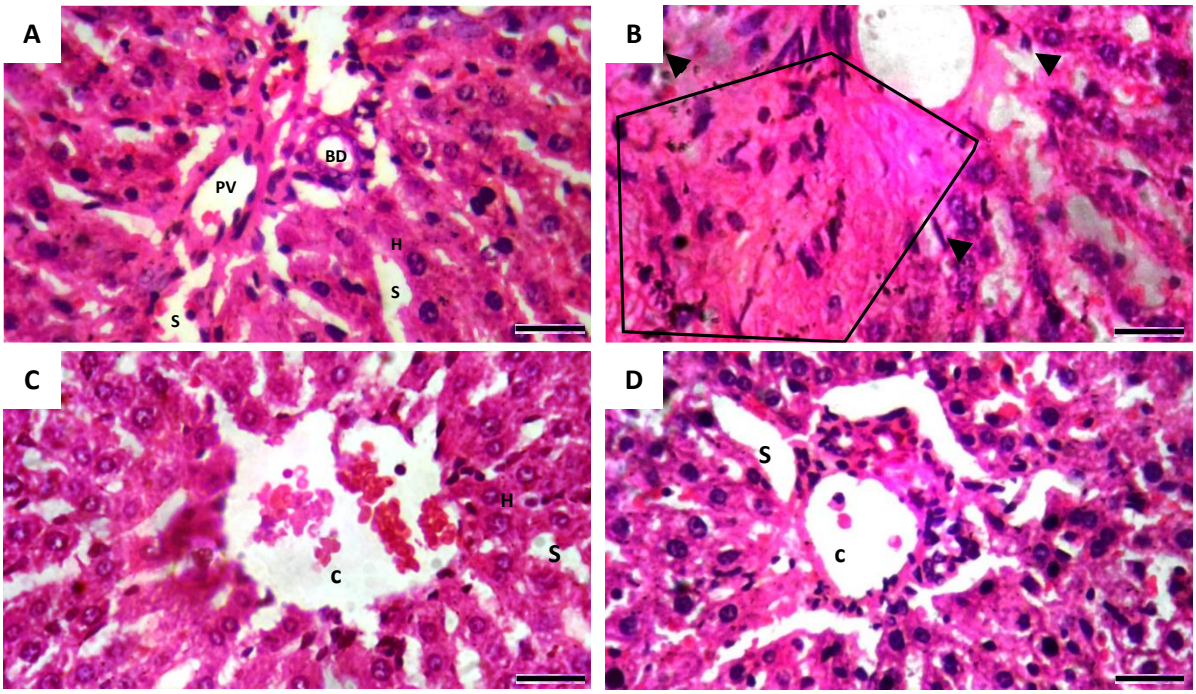

Figure 2: Representative photomicrographs of the liver tissues of all the Experimental groups: A, C and D show normal histological features; radiating hepatocytes (H) with large round nuclei, sinusoids (S), central vein (C), portal vein (PV), and bile duct (BD) while B shows some histological alterations; zonal necrosis, mild Kupfer cell activation (arrowhead). A: control group, B: MSG-treated group, C: MSG + vitamin E- treated group, D: Vitamin E-treated group. (H&E; original objective: 40×; scale bar: 25 µm)

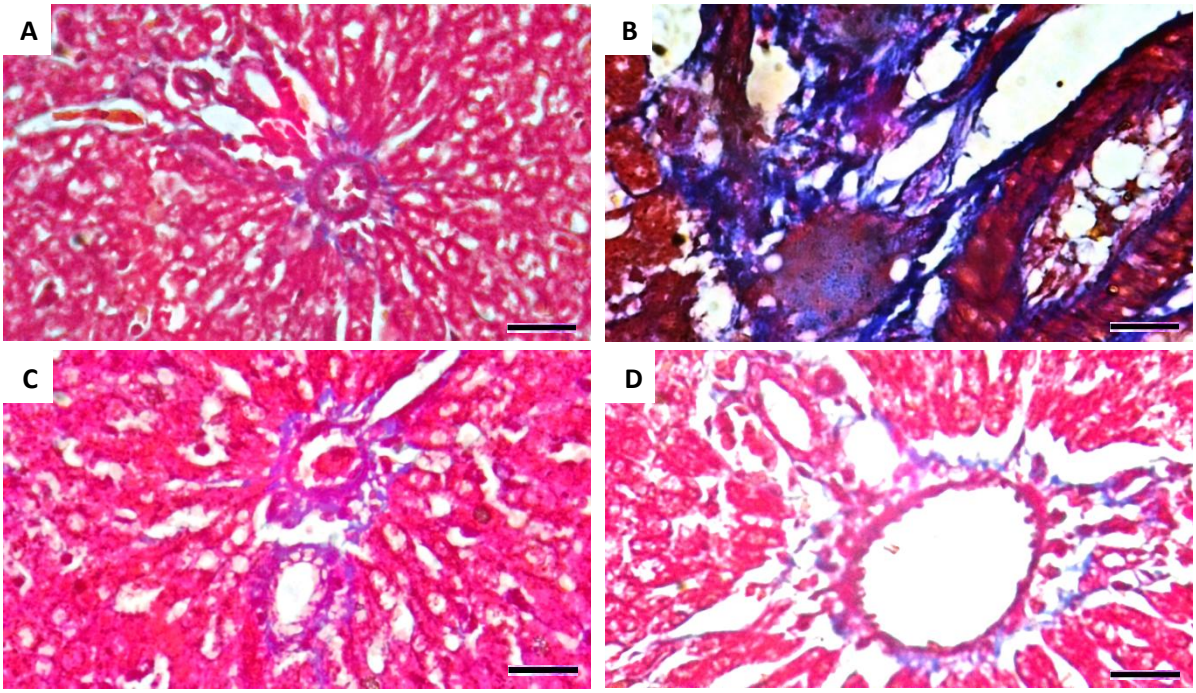

Figure 3: Representative photomicrographs demonstrating collagen deposition in the liver tissues of all the experimental groups: A, C and D show mild collagen deposition around the portal tract (encircled) while B shows dense collagen deposition around the portal tract. A: control group, B: MSG-treated group, C: MSG + Vitamin E-treated group, D: Vitamin E-treated group. (Masson's trichrome; original objective: 40×; scale bar: 25 μm).