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Role of Histological Investigation in The Protective Evaluation of Ginger

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ABSTRACT:
Background: Monosodium glutamate (MSG) usage has been increased in the industry year after year reflecting its crescent use in the food industry. MSG toxicity is specific to the tissue in the body. Herbal drugs provide a managing role for several hepatic disorders so it is critical to find an effective and preventive agent to manage various hepatic insults.
Objective: This experimental study aimed to examine the possible protective effect of ginger extract against injury induced by MSG as a therapeutic agent in pharmaceutical therapies.
Materials and methods: Four groups of rats were divided and obtained treatment periods, after that they conducted serial histological and histochemical changes in control, MSG- and ginger-treated rats, focusing particularly on liver pathology.
Results: MSG exhibited histological and histochemical changes in the liver. Such alterations induced hepatopathology, involving a return to a somewhat normal condition-ginger treatment.
Conclusions: Ginger as herbal supplementations speed up the healing progression of hepatotoxicity. This study reports the effect of ginger exerts anti-toxicity and anti-fibrotic potentials.
Keywords: Monosodium glutamate, Ginger, Histology, Histochemistry.

INTRODUCTION

Monosodium glutamate (MSG) is trusted by some people as a food flavoring that improves the delicacy of cuisine as a nonessential amino acid, L-glutamic acid. It can affect major brain functions including synapses formation and stabilization, memory, cognition, learning, and cell metabolism [(1)].

MSG possesses a certain dose limit because intake is safely recommended by the World Health Organization (WHO) with the Food and Agriculture Organization of United Nations (FAO) for adults in daily intake of less than 2 g sodium (safely one-tenth of a tablespoon) per day [(2)].

The Food and Drug Administrations declared that limited usage of MSG is safe and increased MSG consumption is linked to several potential side effects such as circulatory, cardiac, muscular, neurological, and gastrointestinal disorders. Clinical trials of human and animal subjects also suggested various potential health hazards. The extrapolation of animal model results to humans is more demanding and strenuous [(3)]. Monosodium glutamate use is still considered a controversial source [(4)]. Free radicals are oxidizing agents, and an imbalance in the production/elimination of free radicals (oxygen radicals and other reactive oxygen species (ROS) in cells result in oxidative stress, which destroys macromolecules and essential structures in biological systems[(5)]. Oxidative stress occurs in glutamate excitotoxicity due to increase ROS production and a decrease in the antioxidant defense mechanisms [(6)]. Antioxidants act as free radical scavengers that help to overcome the deteriorating effects of ROS. In this regard, it appears that the use of possible antioxidants has been successful in reversing the effects of MSG [(7)].

The liver is the primary organ of the metabolism and the breakdown of many anticonvulsants, so it is at risk for drug damage and hepatotoxic reactions. The use of spices in the treatment of health problems has been a tradition in the world since early ages. **Su *et al.*** [(8)] stated that dried ginger has therapeutic effects by regulating multiple metabolic pathways. During stressful times, ginger boosts the unique defensive systems of living organisms by increasing their resistance to infections [(9)]. Ginger is used traditionally worldwide for its health endorsing properties such as reducing cardiovascular disease, cancer, diabetes, allergic response, aging, and cancer. It exhibits beneficial effects due to the presence of gingerol and shogaol. They target multiple pathways, inclusive of the cell cycle, apoptotic cell death, and angiogenic pathway [(10)].

However, according to experiments, studies, and applications of traditional medicine and physiotherapy, it is possible to get more benefits for ginger, whether by eating boiled or oil or powder use or in other ways [(11)]. The avoidance of oxidative stress and liver toxicity by ginger can be linked to its antioxidants [(12)].

By inhibiting the activity of enzymes involved in carbohydrate and lipid metabolism, ginger or its active compounds reduced serum lipid and glucose levels, increased lipolysis in the liver and adipose tissue, decreased oxidative stress in white adipose tissue, increased energy metabolism capacity in skeletal muscle, and decreased the expression of

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inflammation-related genes in adipose tissue and liver[13].

This experimental study aimed to examine the possible protective effect of ginger extract against injury induced by MSG as a therapeutic agent in pharmaceutical therapies.

MATERIALS AND METHODS

Preparation of Monosodium glutamate:

Ajinomoto; MSG commercial name was used and dissolved in distilled water and given orally by gavage to rats at a dose of 2.5 g/kg body weight for two weeks according to **John *et al.* [14].**

Preparation of ginger:

The rhizomes of Z. officinale were sold from the local market, shade and dried at room temperature, and were crushed to powder. 125 g of the powder were macerated in 1000 ml of distilled water for 12 h at room temperature and then were filtered through a 5 µm filter to obtain the final aqueous extract. The concentration of the extract is 24 mg/ml equal to 120 mg/kg. Each animal was orally given 1 ml of the final aqueous extract according to **Sakr *et al.* [15].**

Experimental animals and Experimental design:

Experimental animals were randomly divided into four groups; group 1: untreated control rats (C), group 2: ginger group(G): rats were orally administered 1 ml aqueous extract of ginger (24 mg/ml) daily for four weeks by gastric intubation, group 3: monosodium glutamate group (MSG): rats were orally administered with MSG (2.5 g/kg body weight/ day) for two weeks by gastric tube and left without any treatment for another two weeks, and group 4: monosodium glutamate + ginger group (MSG+ G): rats were orally drenched with 1 ml aqueous extract of G (24 mg/ml) and MSG (2.5 g/kg body weight/ day) for two weeks and then with 1 ml aqueous extract of ginger (24 mg/ml) only for another two weeks.

Ethical approval:

A guide to the care of laboratory animals and their use was approved by the National Hepatology and Tropical Medicine Research Institute (NHTMRI; Serial No. A1-2021).

The experimental rats were sacrificed on the 14th and 29th days post-treatment.

Histopathological and histochemical techniques:

Directly, after the animals of all groups were anesthetized, liver tissues were dissected out quickly, apart from liver tissue were prepared for various histological and histochemical studies. livers were immediately excised and fixed in 10% neutral formalin for 24 hours followed by dehydration in ascending grades of alcohol, clearing in xylene, and embedding in paraffin wax. Sections were then cut at 5µ thickness and stained by hematoxylin and eosin stain according to the method reported by **Bancroft and Gamble [16]**, Mallory′s trichrome stain for collagen fibers [17], Periodic acid Schiff's technique for PAS-positive materials [18], Sirius Red staining methods to observe fibrosis levels [19].

RESULTS

Histopathological and histochemical findings:

Hematoxylin and eosin staining:

The histological changes in sections of the liver of the control and treated groups after fourteen and twenty-nine days' post-treatment are shown in **Figure 1.** Normal histological pattern of the liver tissue of a control male rat was observed in **Figure (1A).** Somewhat normal histological pattern was also realized in liver tissue of rats of G groups at the different intervals (**Figure 1B, C).** Examination of the liver tissue after 14 days of treatment with MSG showed many dystrophic changes. These changes included a highly congested hepatic portal vein which contains hemolysed blood cells inside it, thickened wall of the branch of the hepatic artery with a narrow lumen, elongated and stratified wall of bile ducts **(1D)**. In the MSG group after twenty-nine days of treatment liver sections showed numerous deleterious changes such as highly distorted hepatic portal veins with disturbed and ruptured endothelial lining of them with increased proliferation in walls of the bile ducts, dilated hepatic arteries with numerous pyknotic nuclei of hepatocytes **(1E)**. The well-developed architecture of the central area was detected in the liver tissue of rats of group MSG+G after 14 and 29 days of treatment were observed but, some pyknotic nuclei of hepatocytes were still detected **(1F & 1G).**

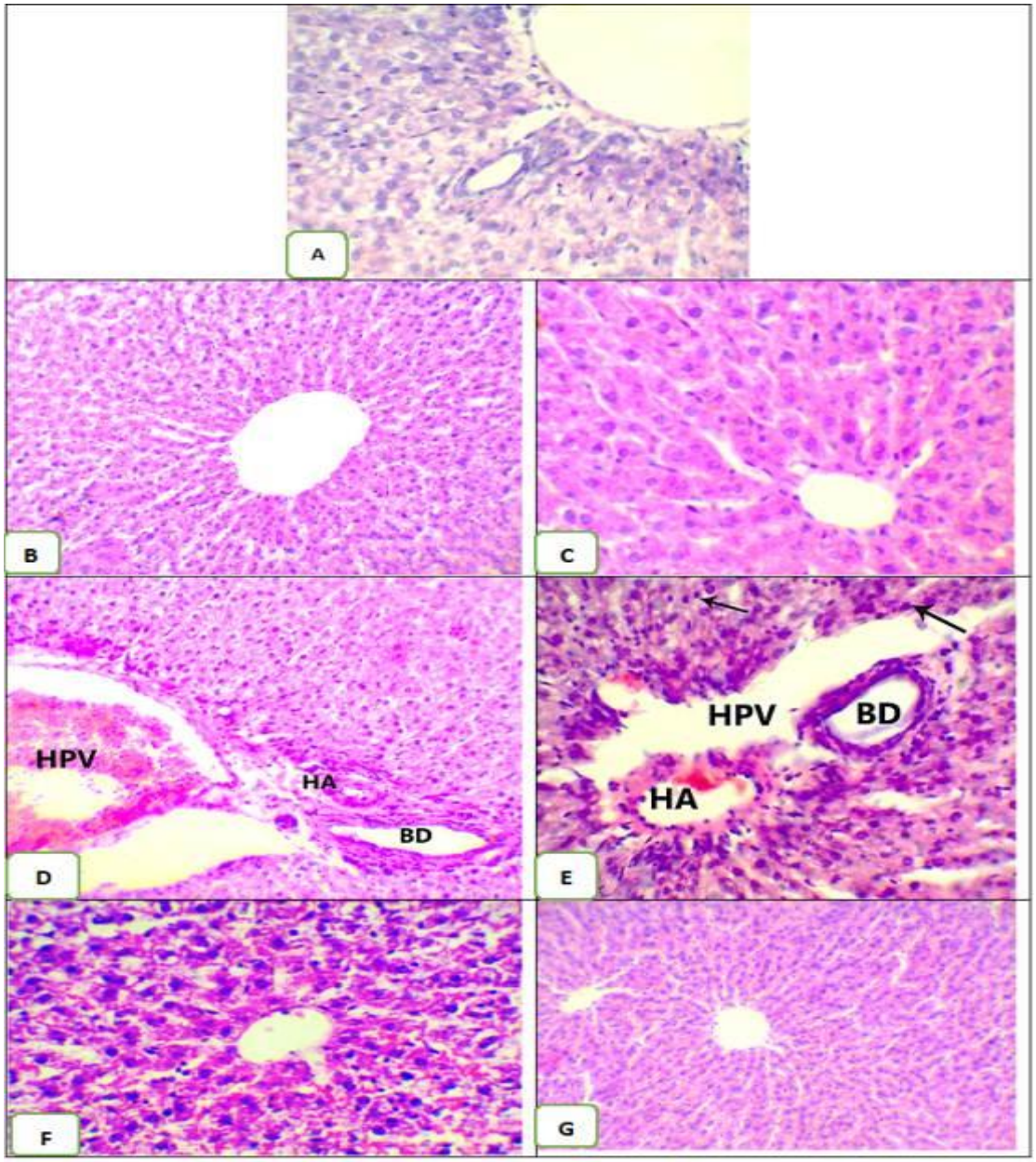

Figure (1): Photomicrographs of sections in the liver tissues of control and treated groups stained with hematoxylin and eosin. **(A)** normal appearance of hepatic tissue in the control livers. **(B, C)** Somewhat normal histological pattern after ginger treatment at the different intervals. **(D)** Examination of the liver tissue after 14 days of treatment with MSG showed many dystrophic changes including, highly congested hepatic portal vein (HPV), thickened wall of the branch of the hepatic artery (HA) with narrow lumen, elongated and stratified wall of bile ducts (BD). **(E)** highly distorted hepatic portal veins (HPV) with disturbed and ruptured endothelial lining of them with increased proliferation in walls of the bile ducts (BD), dilated hepatic arteries (HA) with numerous pyknotic nuclei (→) of hepatocytes. **(F, G)** Well-developed architecture of the central area was detected in the liver tissue of rats of group MSG+G after 14 and 29 days of treatment were observed. H&E stain. (Ax 400; B, C, x200; D x400; E x250; F,Gx200).

Mallory's trichrome staining:

The changes in collagenous fibers distribution in sections of the liver of the control and treated groups after fourteen and twenty-nine days' post-treatment are shown in **Figure 2**. The connective tissue of the control rat liver was demonstrated as a very thin layer of collagenous fibers that support walls of hepatocytes, sinusoidal spaces, and blood vessels (**Figure 2A**). Somewhat normal distribution of collagen fibers around the hepatocytes and the central vein has been detected at 14 and 29 days post-treatment in the ginger groups (**Figure 2B, C**). MSG groups after 14 and 29 days showed numerous scattered collagen fibers in between hepatocytes of the liver tissue and especially in the portal areas (**Figure 2D, E**). Normal distribution of collagen fibers around the hepatocytes was realized in the MSG+G groups at experimental periods (**Figure 2F, G**).

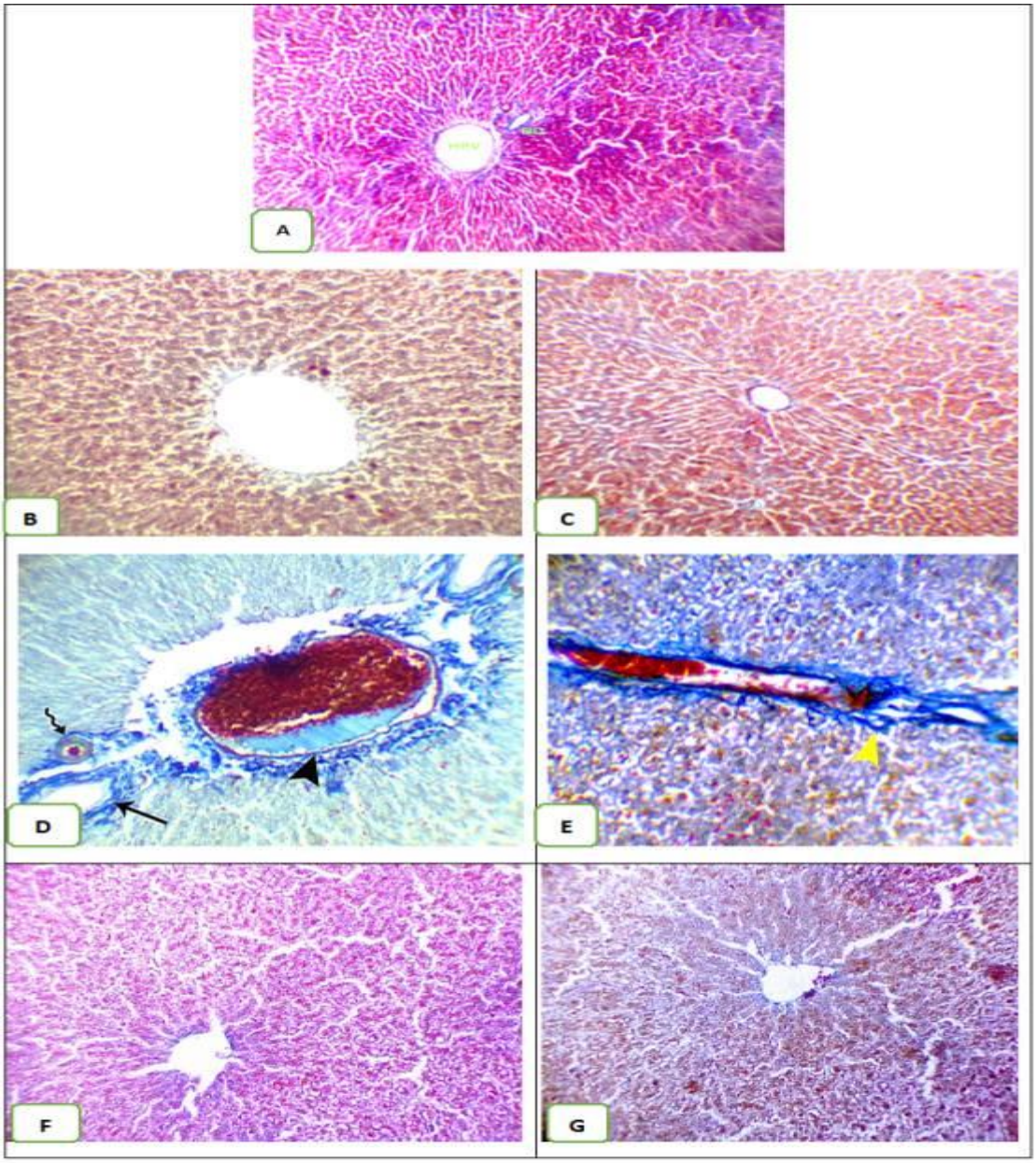

Figure (2): Photomicrographs of sections in the liver tissues of control and treated groups stained with Mallory′s trichrome**. (A)** Connective tissue of the control rat liver was demonstrated as a very thin layer of collagenous fibers supporting walls of hepatocytes, blood sinusoids, bill duct (BD), and hepatic portal vein (HPV). **(B, C)** Normal distribution of collagen fibers around the hepatocytes and the central vein has been detected at 14 and 29 days post-treatment in the ginger groups. **(D, E)** MSG groups after 14 and 29 days showed numerous scattered collagen fibers in between hepatocytes of the liver tissue and especially inside the highly dilated hepatic portal vein (head arrow), walls of the dilated bile ducts (arrow), the arterial walls (corrugated arrow) and in the arterials walls (**yellow** head arrow)**. (F, G).** Normal distribution of collagen fibers in the MSG+G groups at experimental periods. Mallory's trichrome stain. (AX 100; B X200; CX100; D, E X200; F,G x100).

PAS-positive materials:

The changes in PAS-positive materials in sections of the liver of the control and treated groups after fourteen and twenty-nine days' post-treatment are shown in **Figure 3**. The liver tissues of control rats showed heavy glycogen granules filling the cytoplasm of the hepatocytes, walls of the hepatic portal vein, and bile duct diffusely seen throughout the section (**Figure 3A**). Sections in the liver tissue of rats 14th days post- ginger administration showed abundant glycogen content diffusely distributed throughout the hepatic lobules, but rats 29th days post- ginger administration showed nearly normal distribution of glycogen in hepatic cells with a marked PAS reaction around the hepatic portal area **(3B, C)**. MSG group showing depletion of glycogen stores of the liver. Many hepatocytes showed a cytoplasm either partially or completely devoid of glycogen granules in the liver tissues after 14th and 29th days **(3D, E)**. MSG + G shows almost complete restoration of the glycogen content in the hepatocytes in the liver tissues after the 14th and 29th days (**3 F, G**).

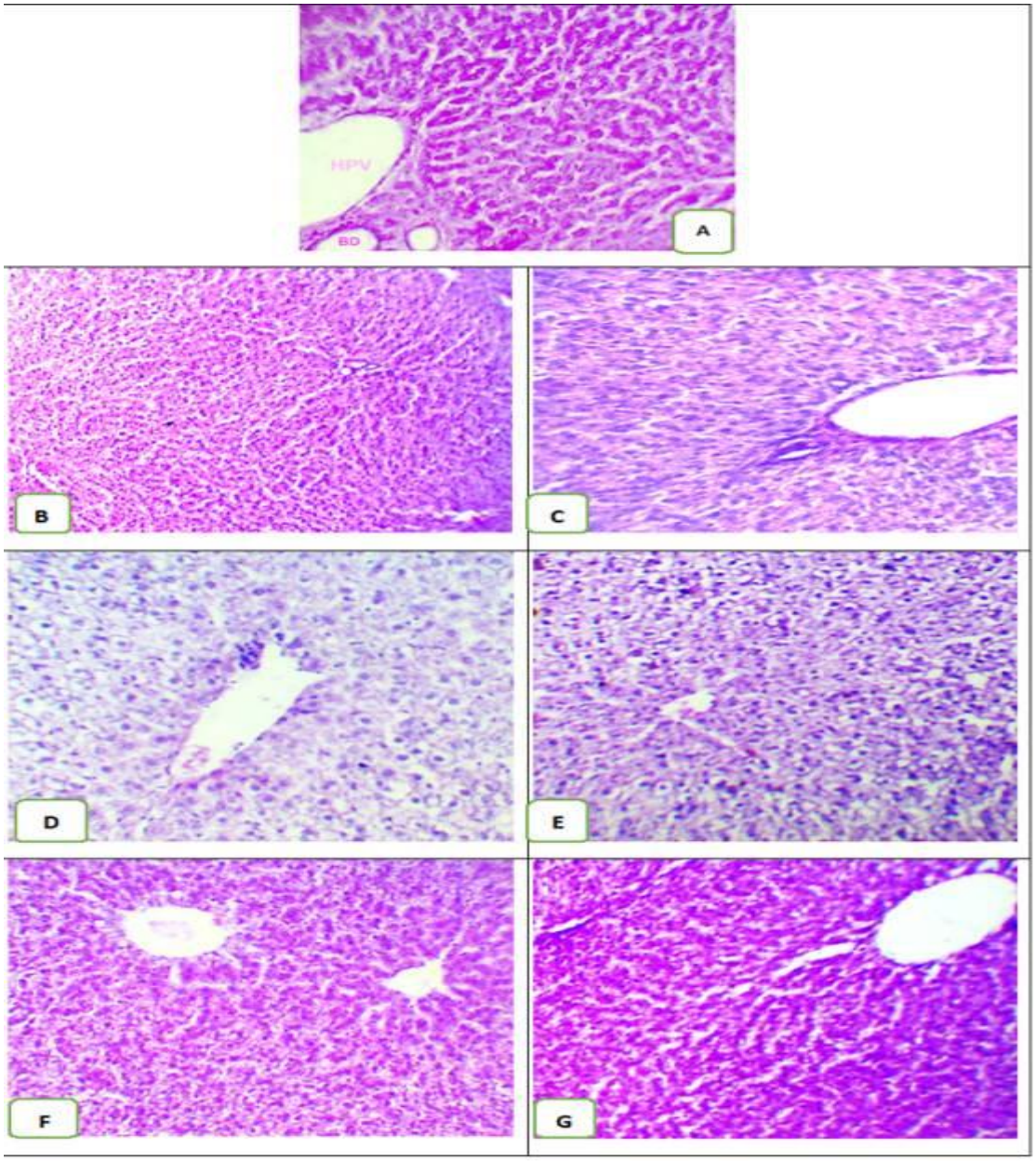

Figure (3): Photomicrographs of sections in the liver tissues of control and treated groups stained with Periodic acid Schiff's technique. (**A**) The liver tissues of control rats show heavy glycogen granules filling hepatocytes, walls of the hepatic portal vein (HPV), and bile ducts (BD). (**B**) Sections in the liver tissue of rats 14th days post- ginger administration showing abundant glycogen content diffusely distributed throughout the hepatic lobules. (**C**) normal distribution of glycogen 29th days post- ginger administration. (**D & E**) MSG group showing depletion of glycogen stores of the liver after 14th and 29th days. (**F & G**) MSG + G showing almost complete restoration of the glycogen. PAS stain. (Magnification is AX200; BX100; C, DX200; EX100; F, G 200X).

Sirius red analysis:

The changes in fibrous tissue content in sections of the liver of the control and treated groups after 14 and 29 days' post-treatment are shown in **Figure 4**. sections in the liver tissues of control rats showing normal content of fibrous tissue in the central and portal areas **(4A)**. liver tissue of rats 14th and 29th days post- ginger administration showing somewhat normal appearance of fibrous tissue around the central vein, hepatic portal vein, hepatic artery, and bile duct **(4 B, C)**. MSG-treated groups all over the experimental period showed increased content of fibrous tissue in and around central veins, hepatic portal area especially around branches of the hepatic artery, hepatic portal vein, and bile ducts **(4 D, E)**. In contrast, the MSG + ginger-treated group observed a somewhat normal content of fibrous tissue in the central areas, and in and around the portal area **(4 F, G)**.

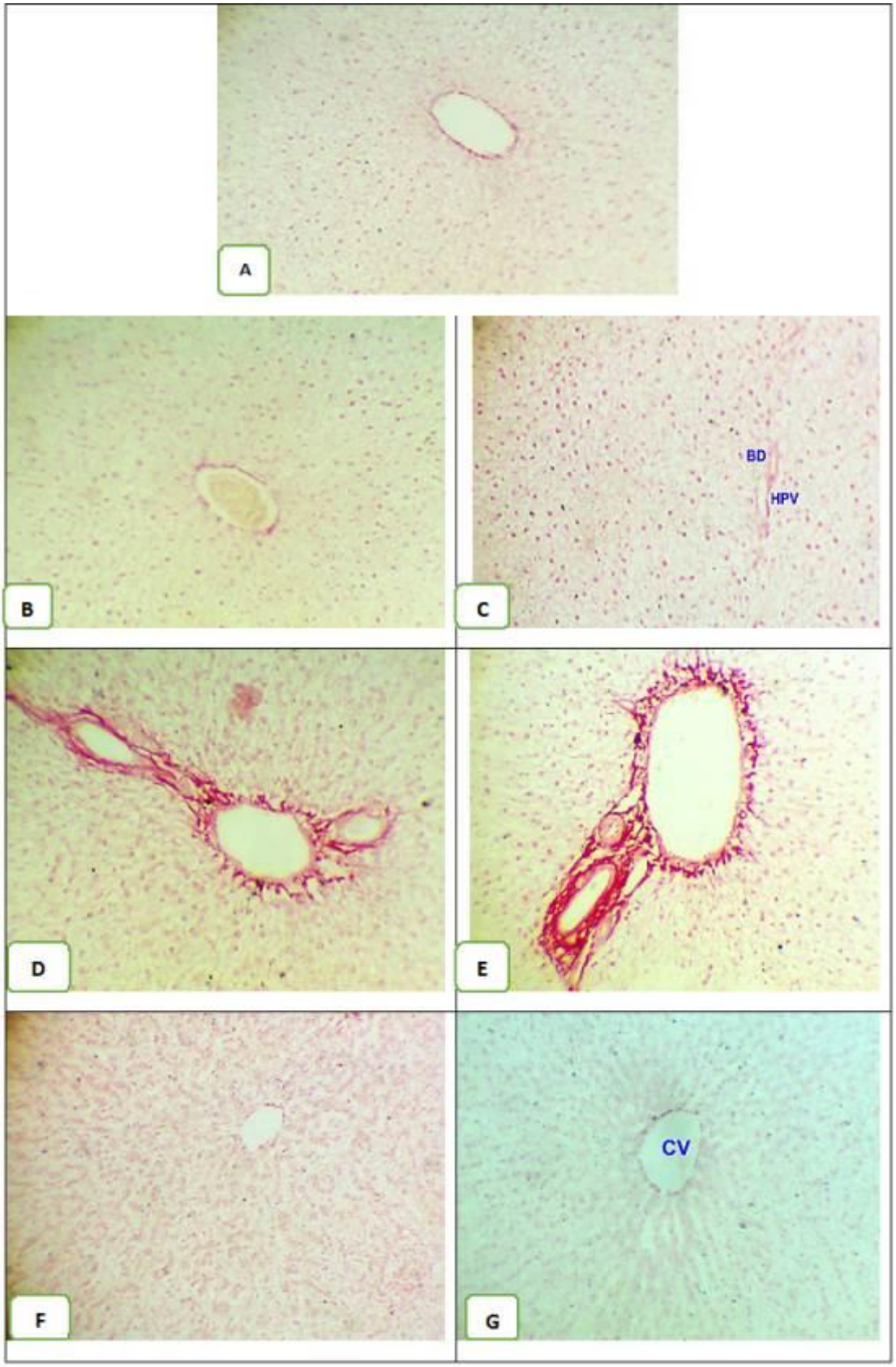

Figure (4): Photomicrographs of sections in the liver tissues of control and treated groups stained with Sirius red. (**A**) control rats showing normal content of fibrous tissue. (**B, C**) 14th and 29th days post- ginger administration showing normal appearance of fibrous tissue around hepatic portal vein (HPV) and bile duct (BD). (**D**, **E**) MSG-treated groups all over the experimental period showed increased content of fibrous tissue. (**F, G**) MSG + ginger-treated group observed somewhat normal content of fibrous tissue, especially around the central vein (CV) after 29 days. Sirius red stain. (A-F x250).

DISCUSSION

Monosodium glutamate has been continuously consumed with no limits via hundreds of food preparations daily. Thus, the safety and toxicity of MSG have become the focus of recent researches [20], especially for the kids who are highly consumed fast food including chips, soups, meats, and canned foods which are marinated by MSG. **Mosallam** [21] found that liver toxicity due to MSG is responsible for more production of ammonium ions and reactive oxygen species. Monosodium glutamate binds to the glutamate receptor and alters the signaling cascade of the hypothalamus. It also disrupts leptin's action, increases the palatability of food, increases pro-inflammatory cytokines, impairs glucose tolerance, increases insulin, leptin, and resistin, respectively, these altered factors ultimately lead to obesity [22]. Ginger rhizome is particularly used as a spice in food by consumers in the world. Ginger blessed with an array of phytochemicals denoted its strong pharmacological potential. Among the different phytochemicals shogaols, gingerols, and zingiberene are considered as most effective [23].

The present results showed a normal histological appearance of the liver tissue after ginger administration at different intervals. Our results are consistent with those obtained by **Mustafa *et al.*** [24] found that rats who received ginger (50 and 100 mg/kg/BW) orally daily for eight weeks showed a normal arrangement of hepatocytes and proper central vein as the control group. These results are supported by the work of **Gad EL-Hak *et al.*** [25] observed that MSG administered orally to the pregnant female rat at a dose of 1 g/5 mL/kg body weight from day 0 to day 20 of pregnancy caused severe fatty degeneration, focal necrosis with a pyknotic nucleus, dilation of sinusoids and infiltration of inflammatory cells in the portal area with proliferation and hyperplasia of the bile duct. Liver sections from the MSG+G group showed well-developed architecture of the central and portal and nearly normal appearance of hepatocytes. Ginger has an antioxidant effect associated with its active ingredients such as gingerols and shogaols which consider the most important components present in the ginger root [26]**. Alsahli *et al.*** [27] found that 6-gingerol has an excellent free radical scavenging activity and this activity was found to be highest at 600 mg/ml. The strong free radical scavenging activity of 6-gingerol indicates its potent antioxidant nature.

Liver fibrosis is one of the most common chronic liver diseases, that related to toxin exposure**.** Our study in the ginger-treated group showed a somewhat normal distribution of collagen fibers. This observation is consistent with the results of **Alsahli *et al.*** [27]**,** who found normal hepatocytes and fewer fibers in the control and 6-Gingerol treated rats groups after treatment with 6-Gingerol at a dose (50 mg/kg body weight) three times a week for 8 weeks. The MSG-treated group showed a significant increase in collagen fibers content. **Al-Salmi *et al.*** [28] observed hepatic fibrosis; this could be due to the decreased production of glutathione peroxidase and the increased MDA level in the liver cells. Moreover, the present data showed that the MSG+G group exhibited a reduction in the fibrous tissue content after 14 and 29 days compared to the control group. In the same line, **Alsahli *et al.*** [27] found that the collagen deposition was significantly decreased with less fibers in rats treated with diethylnitrosamine - plus 6-gingerol at a dose (50 mg/kg body weight) three times in a week for 8 weeks. Overall, these results indicated that ginger therapy reduced the extent to which MSG participates in liver injury, by modulating inflammation and fibrosis.

The present study showed a somewhat normal distribution of PAS-positive materials in the ginger-treated group when compared with controls.

Ismail *et al.* [29] observed that mice fed on standard rodents' basal diet containing ginger powder at a rate of 2% showed increased in the PAS reaction in hepatic cells**.**

Our experiment showed a decrease in PAS reaction throughout the hepatic tissue in the MSG-treated group after 14 and 29 days. **Gad EL-Hak *et al.*** [25] reported marked reduction in the distribution of polysaccharides in the cytoplasm of the hepatocytes after administration of MSG to pregnant female rats at dose 1 g/5 mL/kg body weight from day 0 to day 20 of pregnancy. The decrease of liver polysaccharides by the MSG seems to be through the modification of the enzyme activities of the glycolytic pathway, TCA cycle, gluconeogenesis, and the oxidative phosphorylation **Adeva-Andany *et al.*** [30] or may be through MSG effects on the endocrine system, especially by modification the secretion of glucocorticoids and insulin [31]. MSG + G-treated group after 14 and 29 days showed a decrease in PAS-positive materials compared with the control group. Rats administrated Chlorpyrifos (organophosphate insecticide) and ginger extract at a dose of 750 mg/kg b.w. five days/week for six weeks showed some follicles of the thyroid gland with strong PAS reaction and others with negative PAS reaction [32].

CONCLUSIONS

In conclusion, from the present study, it could be concluded that MSG caused much tissue damage in the hepatic tissue and the administration of ginger has a positive change in the histological and histochemical appearance of hepatic tissues.

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Conflict of interest: Nil.
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