Biochemical Studies on Efficiency of Natural Gum in Chronic Kidney Failure and Liver Cirrhosis in Rats

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ABSTRACT

It is well-established that apoptosis, oxidative stress, and inflammation are associated with several disorders, including chronic renal disease and hepatic disease. Oxidative stress (OS) is a major cause of death from end-stage renal disease which also contributes to atherosclerosis and cardiac issues. The present study aimed to assess the efficacy of Gum Arabic (GA) in mitigating renal damage and hepatotoxicity in rats induced by Chloropyrifos-methyl (CPM). A total of 42 male Wistar rats were divided into seven groups, with four groups (group 2 [IC], group 5 [GA1+IC]a, group 6 [GA2+IC], and group 7 [GA1+IC]b treated with CPM for eight weeks to induce hepatic and renal damage. Two models of GA administration, including the standard oral model in drinking water (15% w/v) and the oral model by gavage at a dose of 1 g/kg body weight were administered. Physiological parameters of kidney and liver functions, including urea, creatinine, AST, and ALT along with anti-oxidant factors (Melaodialdehyde, superoxide dismutase, reduced glutathione, and catalase) were measured in plasma, and homogenates of renal and hepatic tissues on day 57 of the experiment. In addition, histopathological examination was conducted on liver and kidney tissues using hematoxylin and eosin stain to evaluate the efficacy of GA on damaged tissues. Gum Arabic was found to significantly reduce CPM toxic effects in the liver and kidney in groups treated with CPM as liver and kidney parameters were reduced to normal levels. Furthermore, GA reduced histological indicators of inflammation, fibrosis, and apoptosis, as well as renal morphological damage. Additionally, it reduced OS in liver and kidney homogenates. In conclusion, GA effectively reduced the damage that CPM inflicted on liver and kidney tissue by stabilizing physiological parameters to normal levels and repairing cellular structures damaged by OS.

Keywords: Antioxidant, Anti-inflammatory, Gum Arabic, Kidney, Liver, Oxidative stress

INTRODUCTION

In many organisms, oxidative stress (OS) induced by oxygen radicals is a typical response and a crucial biological mechanism in the production of energy (Hajam et al., 2022). Nonetheless, a substantial body of research indicates that the aging process and several diseases including cataracts, cancer, rheumatoid arthritis, the Alzheimer's disease, and atherosclerosis are caused by the unchecked production of free radicals derived from oxygen (Finkel and Holbrook, 2000; Zhu et al., 2004; Luo et al., 2008). Furthermore, individuals with end-stage renal disease (ESRD) may have an accelerated oxidative process (Ali et al., 2020). Chronic kidney disease (CKD), also known as chronic renal failure (CRF), is a serious and expanding public health concern in both industrialized and developing countries (Hussien et al., 2021). Poor health outcomes associated with major non-communicable diseases are thought to be largely caused by CKD (Ayodele and Alebiosu, 2010). The high mortality and distress rates in CKD patients are primarily caused by cardiovascular disease. Inflammation, oxidative stress, and apoptosis are the pathophysiological causes of CKD and its effects (Okamura and Pennathur, 2015). These pathophysiological causes are common in both animals and humans and are important in mediating disease processes (Hajam et al., 2022). The liver is a vital organ that is frequently the target of many toxicants and is actively involved in metabolic processes. One of the main functions of the liver is the detoxification of toxins and xenobiotics (Fan et al., 2021. The chronic liver condition known as hepatic cirrhosis, or cirrhosis, leads to the gradual decline of liver function and the formation of scar tissue rather than healthy liver tissue (David and Hamilton, 2010).

Chlorpyrifos-methyl (CPM; O, O-Dimethyl 0-3, 5, 6-trichloro-2-pyridyl) is an organophosphate (OP) pesticide widely used in agricultural and public health (Hites, 2021). Among agricultural workers and individuals close to application sites, exposure often occurs by accidental ingestion, inhalation, and skin absorption (Ferrer, 2003).

Through oxidative desulfuration, chloropyrifos is physiologically activated to its potentially hazardous form, i.e., chloropyrifos-oxon, by specific cytochrome P450 oxidases found mostly in liver tissue. This may lead to the inhibition of acetylcholinesterase, which is one of the main causes of poisoning from chloropyrifos (Eaton et al., 2008). According to a study, one of the molecular reasons for CPM poisoning is the generation of damaging reactive oxygen species (ROS), which is demonstrated by elevated levels of thiobarbituric acid reactive substances (TBARS) and the oxidative stress that follows in their target organs (Uchendu, et al., 2012). A few examples of ROS are superoxide, hydroxyl radicals, and hydrogen peroxide which are produced during metabolic reactions and interact with lipids, proteins, and DNA in cells to alter their operation (Uzun et al., 2010). Moreover, CPM exhibits lipophilicity and broad binding to biological membranes, specifically to phospholipid bilayers (Morita et al., 2023). It has the potential to cause membrane damage by inducing peroxidation of lipid (LPO; Kalender et al., 2012). Free radical generation is known to cause organ damage, especially hepatotoxicity, prompting research into antioxidant supplementation as a potential substitute for chelating therapy (Heikal, 2012). Consequently, there is a pressing need for natural chemicals that are safe and efficient at scavenging free radicals as an additional tool in the fight against oxidative damage (Patel et al., 2010). The kidneys are extremely fragile and susceptible to damage, as both the renal parenchyma and vasculature can be adversely affected, leading to the loss of some or all renal functions (Russo et al., 2023). Antioxidant research, particularly the discovery of effective natural molecules with low cytotoxicity from plants, has become a significant focus in biomedicine (Tejchman et al., 2021).

The mature sap of *Acacia Senegal* or *Acacia seyal* trees, mostly found in the Sahel region of Sudan, is used to make gum Arabic (GA), a consumable biopolymer. This exudate, which is a thick liquid with a high soluble fiber content, is released by the stems and branches in response to stress factors such as drought, low soil fertility, or damage (Williams and Phillips, 2000). Branching chains of β-d-galactopyranosyl units make up the polysaccharide GA (branches: 21, 22, and 23). Gum Arabic is one of the safest dietary fibers and a valuable food supplement because intestinal bacteria convert it to short-chain fatty acids (SCFAs). Additionally, it contains a lot of calcium, potassium, and magnesium (Ali et al., 2022). Dietary supplementation with GA has been shown to improve high nitrogen discharge and lower serum urea nitrogen levels in patients with chronic renal failure (Hussein et al., 2022). Dietary supplementation with GA also resuts in low serum butyrate, which supports the generation of profibrotic cytokines in the kidneys (Al-Baadani et al., 2021). GA is a combination of macromolecules, mostly proteins, and carbohydrates (Mohammed, 2015). It is utilized as a medication carrier and in pharmaceutical preparations since it is a food supplement that is safe for the body. Additionally, many studies have demonstrated the antioxidant capabilities of GA (Hinson et al., 2004; Trommer and Neubert, 2005; Ali and Al Moundhri, 2006), as well as its involvement in the metabolism of lipids (Evans et al., 1992; Tiss et al., 2001).

The results of treatment for some degenerative diseases, like renal failure, have been positive (Matsumoto et al., 2006; Ali et al., 2008). This is also true for heart implications (Glover et al., 2009) and digestive disorders (Rehman et al., 2003; Wapnir et al., 2008). Thus, there is compelling evidence that in addition to its well-known emulsifying properties, GA can have beneficial health effects as well (Montenegro et al., 2012). In studies assessing the risk associated with the liver, heart, and kidneys, research has indicated that GA decreases blood pressure and plasma cholesterol in rats, promotes tooth demineralization, inhibits microbial development, and enhances intestinal absorption, all of which contribute to a decrease in diarrhea (Kamal et al., 2021).

The administration of GA in mice has been found to decrease intestinal sodium expression, leading to delayed glucose transport, hyperglycemia, hyperinsulinemia, and increased body weight (Dashtdar and Kardi, 2018). Additionally, GA has shown promise in the treatment of colorectal carcinogenesis, a condition marked by the progressive accumulation of several genetic changes. Tumor suppressor genes become inactive due to mutations in the *p53* and *Kras* genes, while oncogenes (antagonists) become active, directly contributing to the occurrence of colorectal cancer (Melo et al., 2023).

The present study aims to assess the antioxidant capacity of GA against oxidative stress in hepatic and renal tissues in Wistar lab rats.

MATERIALS AND METHODS

Ethical approval

The World Organization for Animal Health (WOAH), Cairo University's Institutional Animal Care and Use Committee (CU-IACUC) guidelines at Cairo University, Cairo, Egypt, official Ministry of Agriculture Decree No. 27, 1967, and the Guide for the Care and Use of Laboratory Animals, 8th Edition 2011 (the Guide) were all consulted in the preparation of this report.

Animals

A total of 42 male Wistar albino rats (n = 42), approximately 200 ± 10 g, 9–10 weeks old, were obtained from the Animal House of the Agricultural Research Center in Dokki, Giza Governorate, Egypt. The rats were maintained under a 12-hour light-dark cycle, at a temperature of $24 \pm 2°C$, and a relative humidity of 60%. They were provided with regular mouse food and had unrestricted access to water.

Experimental design

The acclimatization period was two weeks to stabilize all metabolic conditions. A total of 42 rats were treated for eight weeks using the following protocol after being assigned to seven equal groups (6 rats per group). Group 1 (Normal control; NC) was fed a normal diet until the end of the study (8 weeks). Group 2 (Injury control; IC) received a normal diet plus an oral dose of CPM (O, O-Dimethyl 0-3, 5, 6-trichloro-2-pyridyl phosphorothioate; Reldan® 22.5% Emulsifiable Concentrate "EC"), at 1/50 of LD_{50} (3129 mg/kg) daily for eight weeks. Group 3 (gum Arabic1; GA1) was fed a regular diet plus oral GA at a rate of 1 g/kg body weight daily for eight weeks. Group 4 (gum Arabic2; GA2) was given normal rat feed and 15% weight/volume of GA in drinking water daily for eight weeks. Group 5 (GA1+IC)a received the same daily amount of CPM as Group 2 (IC), a normal feed, and GA as Group 3 (GA1) for the same period of time. Group 6 (GA2+IC) received normal feed and CPM as in Group 2 (IC), plus GA as in Group 4 (GA2) for eight weeks. Group 7 (GA1+IC)b was given normal feed plus CPM as in Group 2 (IC) for four weeks, followed by the GA dose used in Group 3 (GA1) for an additional four weeks. Throughout the treatment phase, rats underwent weekly weighting.

Blood sampling and tissue retrieval

On day 57, 3 ml blood samples were collected from overnight-fasted rats using capillary glass tubes from the retro-orbital plexus. Plain tubes were kept dry and clean for 30 minutes to allow blood clotting before being centrifuged at 3000 rpm. The resulting serum was then utilized to measure the lipid profile, liver function, and kidney function by assaying the physiological parameters using a Cobas C11 blood chemistry analyzer. Liver and kidney tissue samples were retrieved from all animals in the seven groups of the experiment after anesthetizing them with ketamine (Ketalar 10 mg/ml injection by Pfizer Limited) at a dose of 100 mg/kg body weight, and then all 42 animals were dissected.

Evaluation of kidney and liver antioxidant enzymes

Malondialdehyde (MDA), superoxide dismutase (SOD), reduced glutathione (GSH), and catalase (CAT) levels in renal and hepatic tissues were determined using Total Antioxidant Capacity (TAC) Assay Kit by Abbexa, United Kingdom.

Histopathological examination

Small portions of kidney and liver tissue were cut, quickly fixed with 10% neutral buffered formalin, and then embedded in paraffin wax. Subsequently, paraffin blocks from the kidney and liver were sectioned using a microtome to create 4-μm thin slices. These slices were placed on slides and stained with hematoxylin-eosin. Then slides were then examined using a Leica DM 2500 with a mounted Leica DFC 290HD digital camera, Germany.

Statistical analysis

Data are presented as the mean ± standard error. Statistical comparisons between different groups were conducted using one-way analysis of variance (ANOVA). Statistical analyses were performed using the Statistical Package for the Social Science (SPSS) software, version 22.0 (SPSS Inc., Chicago, IL, USA). Significant differences were determined using T-test at a significance level of $p < 0.05$. Values are expressed as the mean ± standard error of the mean (Levesque, 2007).

RESULTS

Physiological data

The results in Figure 1 show that the injury control (IC) rats treated with CPM and the rats treated with GA separately or in combination with other groups experienced a significant decrease in weight gain ($p < 0.05$). In contrast to group 1 (NC), the organ weights of the rats administered with CPM alone increased significantly compared to Group 1 (NC) and the other groups that received GA alone or CPM ($p < 0.05$, Table 1).
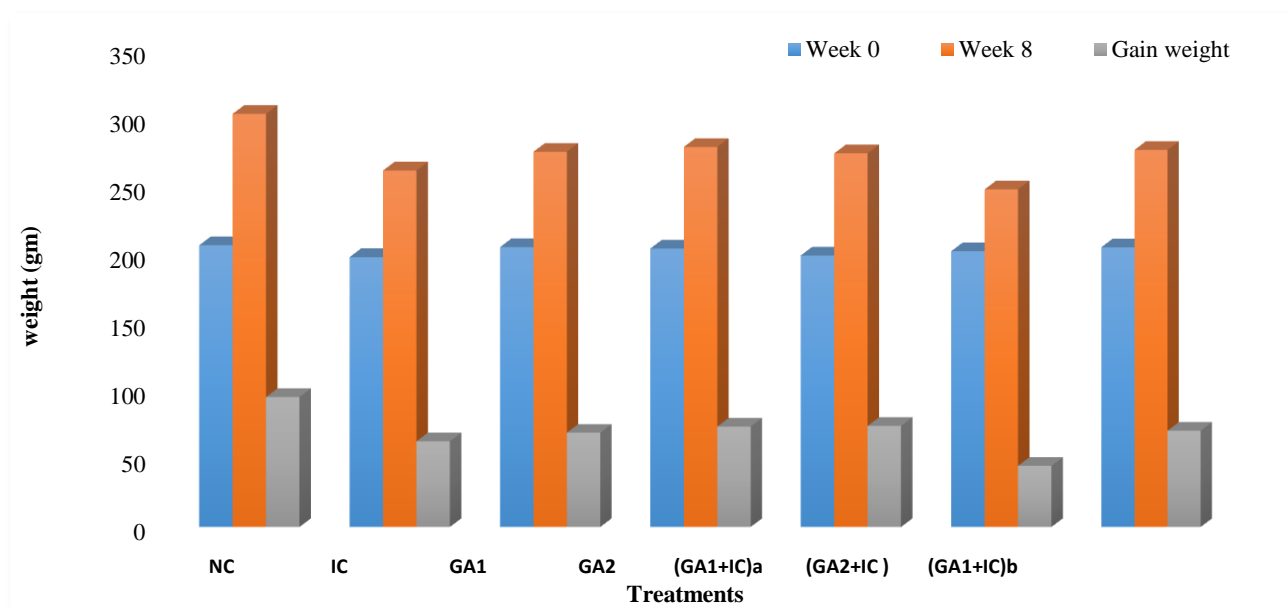
Figure 1. The affected rats' weight by administrating chlorpyrifos-methyl to induce oxidative stress and treatment by different groups. GA: Group 1 (NC): Control group, Group 2 (IC): Rats which administered CPM (3129 mg/kg) daily for 8 weeks, Group 3 (GA1): Rats which received normal GA feed 1 gm/kg body weight daily for 8 weeks, Group 4 (GA2): Rats which administered GA 15% w/v in drinking water daily for 8 weeks, Group 5 (GA1+IC)a: Rats which received normal feed and CPM (3129 mg/kg) plus GA (1 gm/kg body weight) daily for 8 weeks, Group 6 (GA2+IC): Rats which received normal feed and CPM (3129 mg/kg) plus GA 15% w/v in drinking water daily for 8 weeks, Group 7 (GA1+IC)b: Rats which received normal feed plus CPM for 4 weeks, then treated with GA (1 gm/kg body weight) for 4 weeks.

Table 1. Administration effect of chlorpyrifos-methyl and gum Arabic on weight gained of rats aged 4 months in the experimental groups

Parameters \ Treatments	Group 1 (NC)	Group 2 (IC)	Group 3 (GA1)	Group 4 (GA2)	Group 5 (GA1+IC)a	Group 6 (GA2+IC)	Group 7 (GA1+IC)b
Week 0 weight (g)	207.2	198.5	205.8	204.8	199.7	202.8	205.7
Week 8 weight (g)	303.2	261.8	275.5	279	274.3	248	276.8
Gain weight (g)	96	63.33	69.67	74.17	74.67	45.17	71.17

Group 1 (NC): Control group, Group 2 (IC): Rats which administered CPM (3129 mg/kg) daily for 8 weeks, Group 3 (GA1): Rats which received normal GA feed 1 gm/kg body weight daily for 8 weeks, Group 4 (GA2): Rats which administered GA 15% w/v in drinking water daily for 8 weeks, Group 5 (GA1+IC)a: Rats which received normal feed and CPM (3129 mg/kg) plus GA (1 gm/kg body weight) daily for 8 weeks, Group 6 (GA2+IC): Rats which received normal feed and CPM (3129 mg/kg) plus GA 15% w/v in drinking water daily for 8 weeks, Group 7 (GA1+IC)b: Rats which received normal feed plus CPM for 4 weeks, then treated with GA (1 gm/kg body weight) for 4 weeks.

Liver biochemical parameters

The results in Figures 2A and 2B show that CPM administration in Group 2 (IC) significantly increased the activities of liver function parameters such as ALT, AST, and Total Bilirubin compared to control Group 1 (NC; Figure 3A, $p < 0.05$). However, the CPM Group 2 (IC) revealed a significant decrease in Total Protein in comparison with Group 1 (NC), indicating hepatocellular damage ($p < 0.05$). This negative effect was mitigated in the groups that received CPM combined with GA (Figure 3B). A slight increase was observed in ALT activity in Group 3 (GA1) which received GA (Figure 2A, $p > 0.05$). In summary, the results indicate a positive effect of GA on liver functions in groups that received GA treatment either alone or in combination with CPM, compared to Group 2 (IC), which received only CPM and exhibited liver toxicity (Table 2).

Renal biochemical parameters

Given that Group 2 (IC) has significantly higher serum creatinine and urea values than the other groups, data in Figure 4 shows that CPM significantly increased these parameters ($p < 0.05$). This increase is indicative of renal damage and kidney dysfunction caused by toxicity from CPM. The renal parameters significantly improved in all groups that drank water containing GA compared to Group 2 (IC) ($p < 0.05$, Table 2).

Lipids profile in serum of the experimental groups

In comparison to Group 1 (NC), the CPM Group 2 (IC) data showed a significant decrease in HDL but a notable increase in triglycerides (TG), LDL, and VLDL ($p < 0.05$). However, the groups that received GA treatment had a

significant improvement in lipid profile characteristics, indicating that GA has a promising potential for treating elevated lipid profile parameters (Figure 5, p < 0.05, Table 2).

Antioxidant parameters in liver and kidney tissues

The results represented in figures 6 and 7 show a notable decrease in GSH, SOD and Catalase levels in the liver and kidney tissues of the CPM Group 2 (IC) compared to Group 1 (NC). This decrease provides clear evidence of improvement as a result of the GA administration in other groups (p < 0.05). Administration of GA showed insignificant changes compared to the NC Group 1 (p > 0.05), with a slight increase in Catalase (Figure 6A) and GSH (Figure 6B) compared to the NC Group (p > 0.05). On the other hand, the CPM Group showed increased levels of MDA and SOD in the liver and kidney tissues, indicating heightened oxidative stress via the administration of GA in other groups (GA1; GA2; (GA1+IC)a; (GA2+IC): (GA1+IC)b) as represented in Figure 7 (p < 0.05).
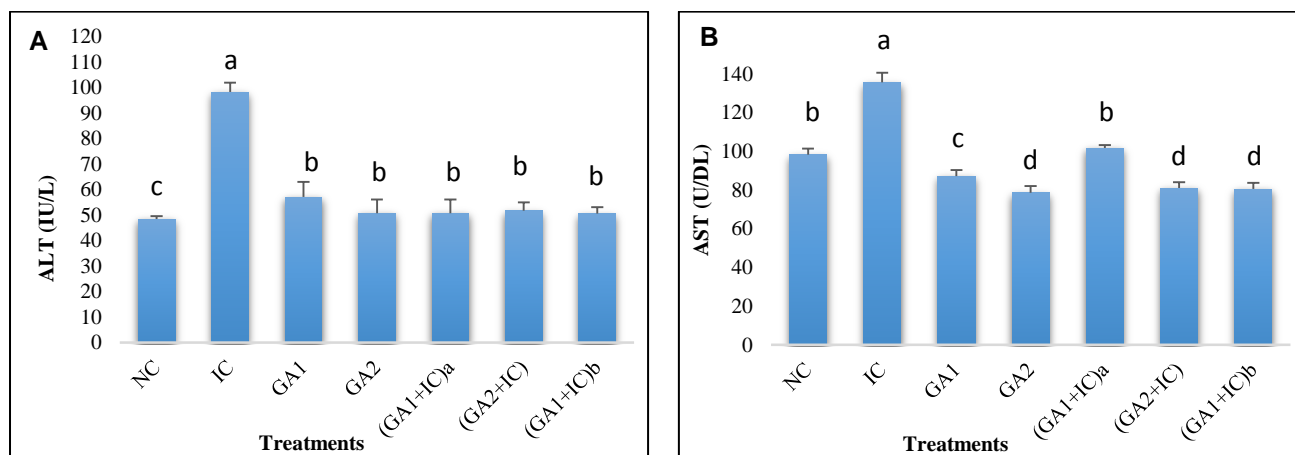

Figure 2. The rats' liver enzymes as a result of administrating chlorpyrifos-methyl to induce oxidative stress, and gum Arabic treatment. A: ALT level difference in serum, B: AST level difference in serum, Group 1 (NC): Control group, Group 2 (IC): Rats which administered CPM (3129 mg/kg) daily for 8 weeks, Group 3 (GA1): Rats which received normal GA feed 1 gm/kg body weight daily for 8 weeks, Group 4 (GA2): Rats which administered GA 15% w/v in drinking water daily for 8 weeks, Group 5 (GA1+IC)a: Rats which received normal feed and CPM (3129 mg/kg) plus GA (1 gm/kg body weight) daily for 8 weeks, Group 6 (GA2+IC): Rats which received normal feed and CPM (3129 mg/kg) plus GA 15% w/v in drinking water daily for 8 weeks, Group 7 (GA1+IC)b: Rats which received normal feed plus CPM for 4 weeks, then treated with GA (1 gm/kg body weight) for 4 weeks.

Table 2. Physiological parameters of the experimental groups as a result of chlorpyrifos-methyl administration and gum Arabic treatment in rats aged 4 months

Treatments / Parameters	Group 1 (NC)	Group 2 (IC)	Group 3 (GA1)	Group 4 (GA2)	Group 5 (GA1+IC)a	Group 6 (GA2+IC)	Group 7 (GA1+IC)b
Urea (mmol/L)	58 ± 1^b	76 ± 3^a	42 ± 7^c	43 ± 5^c	57 ± 3^b	56 ± 3^b	59 ± 1^b
Creatinine (mg/dL)	0.56 ± 0.11^c	1.71 ± 0.12^a	0.50 ± 0.09^c	0.47 ± 0.12^c	0.47 ± 0.03^c	0.5 ± 0.04^c	0.68 ± 0.02^b
Cholesterol (Chol) (mg/dl)	56.90 ± 1.5^d	99.35 ± 1.4^a	47.52 ± 0.94^f	52.22 ± 0.82^e	69.81 ± 1.0^b	58.27 ± 0.96^e	64.43 ± 0.68^c
Triglycerides (TG) (mg/dl)	45.82 ± 0.4^d	79.88 ± 2.5^a	37.45 ± 2.8^e	47.37 ± 2.8^d	56.04 ± 2.7^{bc}	50.65 ± 2.7^{cd}	62.00 ± 2.6^b
Total protein (TP) (g/dl)	5.56 ± 0.17^a	4.29 ± 0.11^d	5.44 ± 0.15^{ab}	5.24 ± 0.33^{ab}	4.65 ± 0.47^{cd}	5.53 ± 0.34^a	4.96 ± 0.32^{bc}
Albumin (Alb) (g/dl)	2.86 ± 0.07^a	2.53 ± 0.04^c	2.79 ± 0.02^b	2.75 ± 0.02^b	2.73 ± 0.04^b	2.72 ± 0.07^b	2.58 ± 0.05^c
Total Bilirubin	0.19 ± 0.02^d	0.61 ± 0.02^a	0.23 ± 0.01^c	0.26 ± 0.00^b	0.16 ± 0.02^e	0.16 ± 0.00^{de}	0.23 ± 0.00^{bc}
Alanine transaminase (ALT) (U/L)	48.48 ± 1.1^c	98.27 ± 3.7^a	57.12 ± 5.9^b	50.70 ± 5.5^{bc}	50.70 ± 5.5^{bc}	51.80 ± 3.2^{bc}	50.60 ± 2.6^{bc}
Aspartate aminotransferase (AST) (U/L)	98.33 ± 3.1^b	135.69 ± 4.9^a	87.30 ± 3.1^c	78.67 ± 3.4^d	101.74 ± 1.6^b	81.06 ± 3.0^d	80.57 ± 3.1^d

[a, b, c, d, e, f]: Indicate that different letters in the same row differ at (p < 0.05). Group 1 (NC): Control group, Group 2 (IC): Rats which administered CPM (3129 mg/kg) daily for 8 weeks, Group 3 (GA1): Rats which received normal GA feed 1 gm/kg body weight daily for 8 weeks, Group 4 (GA2): Rats which administered GA 15% w/v in drinking water daily for 8 weeks, Group 5 (GA1+IC)a: Rats which received normal feed and CPM (3129 mg/kg) plus GA (1 gm/kg body weight) daily for 8 weeks, Group 6 (GA2+IC): Rats which received normal feed and CPM (3129 mg/kg) plus GA 15% w/v in drinking water daily for 8 weeks, Group 7 (GA1+IC)b: Rats which received normal feed plus CPM for 4 weeks, then treated with GA (1 gm/kg body weight) for 4 weeks.
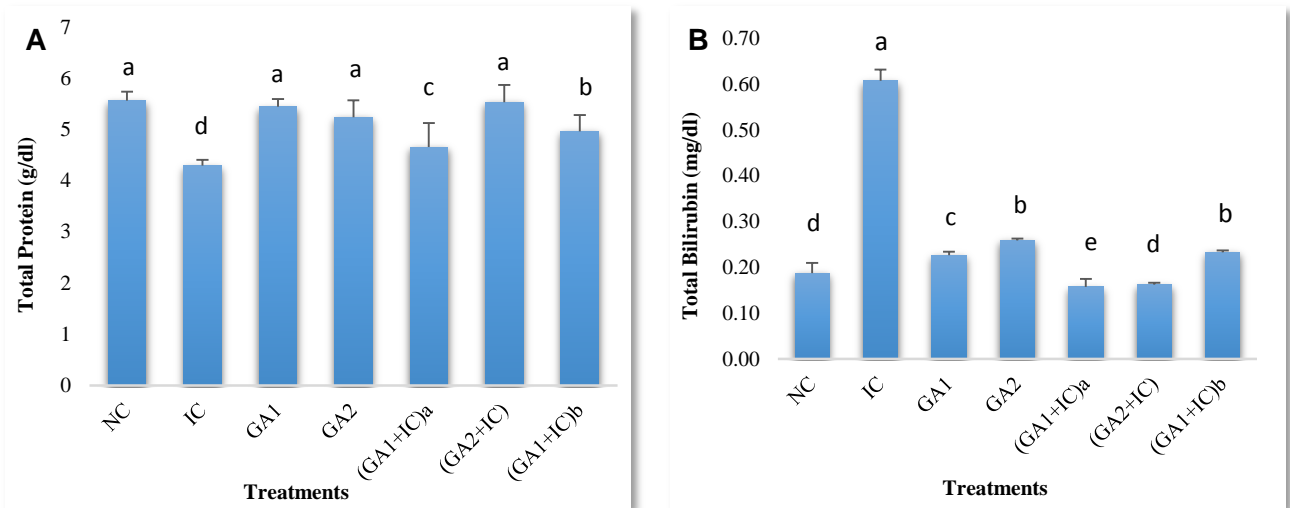
Figure 3. The rats' liver parameters were affected by chlorpyrifos-methyl administration as oxidative stress and gum Arabic treatment. A: Total protein level in serum, B: Total bilirubin level in serum, Group 1 (NC): Control group, Group 2 (IC): Rats which administered CPM (3129 mg/kg) daily for 8 weeks, Group 3 (GA1): Rats which received normal GA feed 1 gm/kg body weight daily for 8 weeks, Group 4 (GA2): Rats which administered GA 15% w/v in drinking water daily for 8 weeks, Group 5 (GA1+IC)a: Rats which received normal feed and CPM (3129 mg/kg) plus GA (1 gm/kg body weight) daily for 8 weeks, Group 6 (GA2+IC): Rats which received normal feed and CPM (3129 mg/kg) plus GA 15% w/v in drinking water daily for 8 weeks, Group 7 (GA1+IC)b: Rats which received normal feed plus CPM for 4 weeks, then treated with GA (1 gm/kg body weight) for 4 weeks.
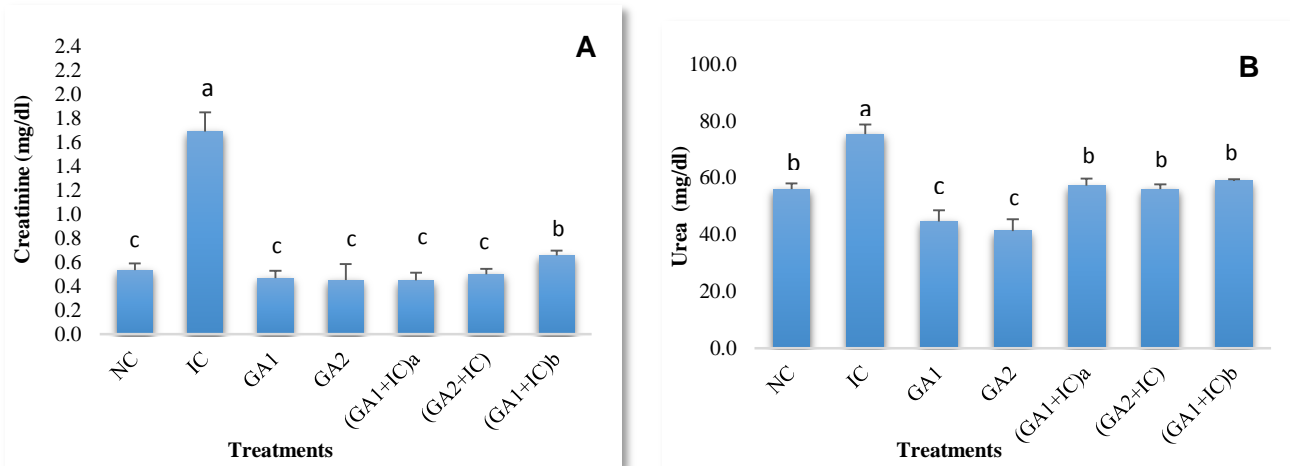

Figure 4. Renal function of rats administered chlorpyrifos-methyl to induce oxidative stress in the kidney, and its effects were countered by gum Arabic treatment. A: Serum creatinine level, B: Blood urea level, Group 1 (NC): Control group, Group 2 (IC): Rats which administered CPM (3129 mg/kg) daily for 8 weeks, Group 3 (GA1): Rats which received normal GA feed 1 gm/kg body weight daily for 8 weeks, Group 4 (GA2): Rats which administered GA 15% w/v in drinking water daily for 8 weeks, Group 5 (GA1+IC)a: Rats which received normal feed and CPM (3129 mg/kg) plus GA (1 gm/kg body weight) daily for 8 weeks, Group 6 (GA2+IC): Rats which received normal feed and CPM (3129 mg/kg) plus GA 15% w/v in drinking water daily for 8 weeks, Group 7 (GA1+IC)b: Rats which received normal feed plus CPM for 4 weeks, then treated with GA (1 gm/kg body weight) for 4 weeks.
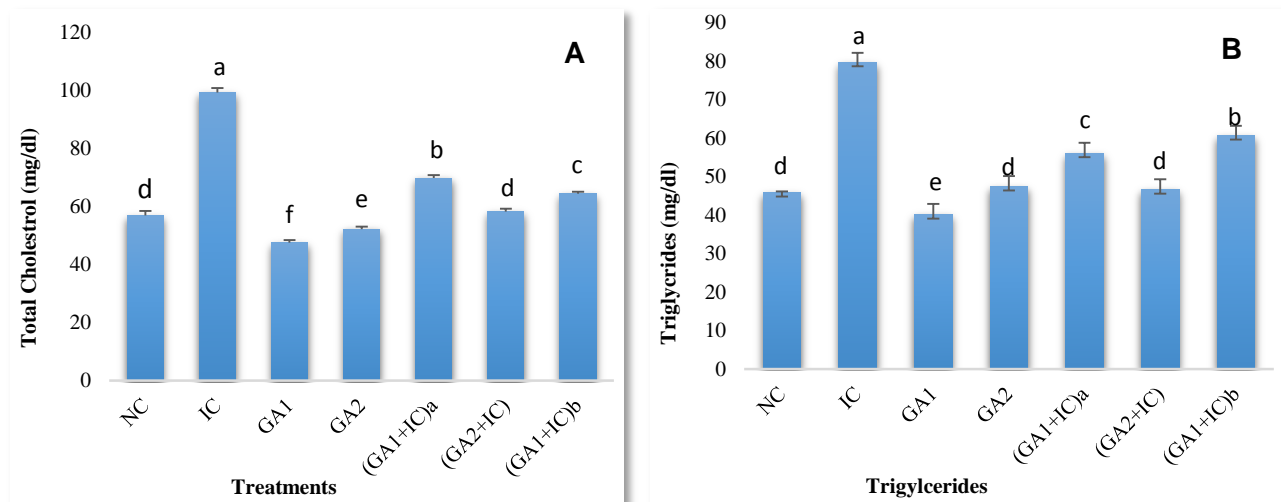
Figure 5. The effects on lipid profile of rats affected by chlorpyrifos-methyl administration countered by gum Arabic treatment. A: Total cholesterol in serum, B: Triglycerides in serum, Group 1 (NC): Control group, Group 2 (IC): Rats which administered CPM (3129 mg/kg) daily for 8 weeks, Group 3 (GA1): Rats which received normal GA feed 1 gm/kg body weight daily for 8 weeks, Group 4 (GA2): Rats which administered GA 15% w/v in drinking water daily for 8 weeks, Group 5 (GA1+IC)a: Rats which received normal feed and CPM (3129 mg/kg) plus GA (1 gm/kg body weight) daily for 8 weeks, Group 6 (GA2+IC): Rats which received normal feed and CPM (3129 mg/kg) plus GA 15% w/v in drinking water daily for 8 weeks, Group 7 (GA1+IC)b: Rats which received normal feed plus CPM for 4 weeks, then treated with GA (1 gm/kg body weight) for 4 weeks.
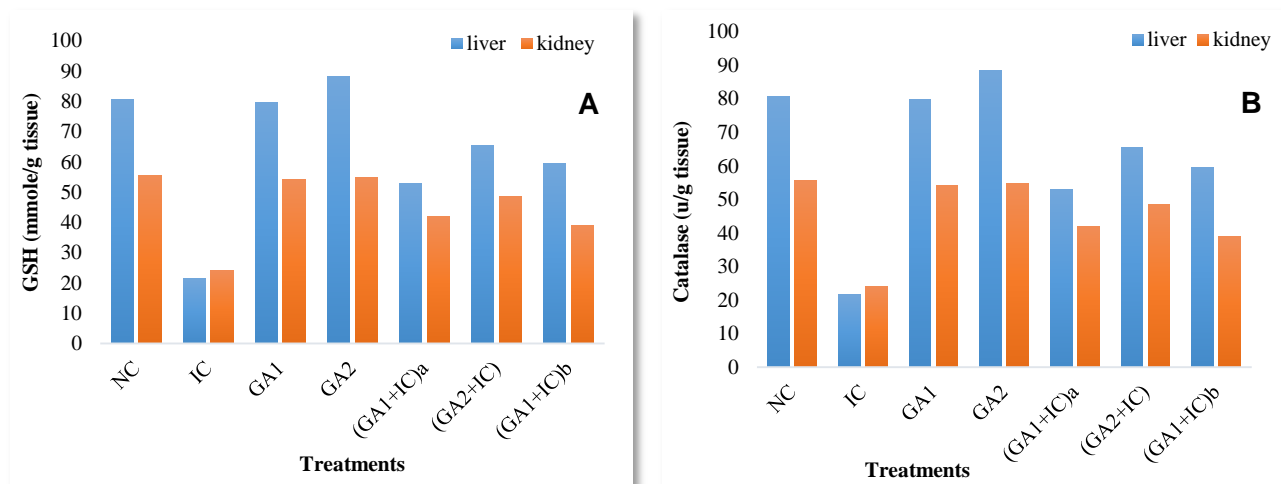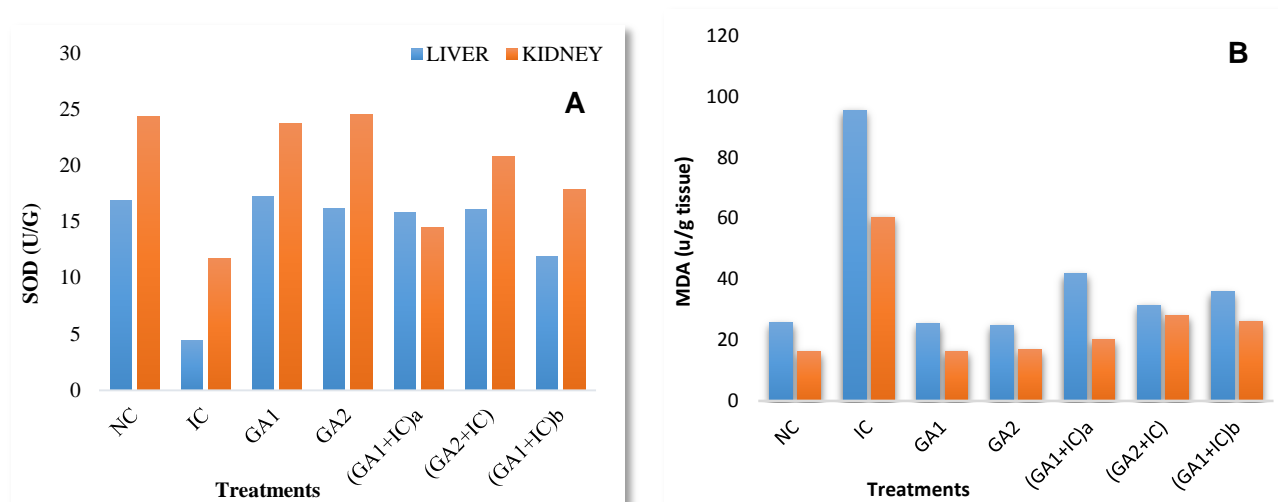

Figure 6. Reduced glutathione and catalase level differences in liver and kidney homogenates of rats in rats treated with chlorpyrifos-methyl in comparison with rats treated with gum Arabic. A: Reduced glutathione (GSH) level difference, B: Catalase (CAT) level difference, Group 1 (NC): Control group, Group 2 (IC): Rats which administered CPM (3129 mg/kg) daily for 8 weeks, Group 3 (GA1): Rats which received normal GA feed 1 gm/kg body weight daily for 8 weeks, Group 4 (GA2): Rats which administered GA 15% w/v in drinking water daily for 8 weeks, Group 5 (GA1+IC)a: Rats which received normal feed and CPM (3129 mg/kg) plus GA (1 gm/kg body weight) daily for 8 weeks, Group 6 (GA2+IC): Rats which received normal feed and CPM (3129 mg/kg) plus GA 15% w/v in drinking water daily for 8 weeks, Group 7 (GA1+IC)b: Rats which received normal feed plus CPM for 4 weeks, then treated with GA (1 gm/kg body weight) for 4 weeks.

Figure 7. Superoxide dismutase and Melondialdehyde level in liver and kidney homogenates of rats treated with chlorpyrifos-methyl in comparison with rats treated with gum Arabic. A: Superoxide dismutase (SOD) level difference, B: Melondialdehyde (MDA) level difference, Group 1 (NC): Control group, Group 2 (IC): Rats which administered CPM (3129 mg/kg) daily for 8 weeks, Group 3 (GA1): Rats which received normal GA feed 1 gm/kg body weight daily for 8 weeks, Group 4 (GA2): Rats which administered GA 15% w/v in drinking water daily for 8 weeks, Group 5 (GA1+IC)a: Rats which received normal feed and CPM (3129 mg/kg) plus GA (1 gm/kg body weight) daily for 8 weeks, Group 6 (GA2+IC): Rats which received normal feed and CPM (3129 mg/kg) plus GA 15% w/v in drinking water daily for 8 weeks, Group 7 (GA1+IC)b: Rats which received normal feed plus CPM for 4 weeks, then treated with GA (1 gm/kg body weight) for 4 weeks.

Histopathological examination of liver tissue

The histopathological analysis of liver tissues in Group 1 (NC) revealed a normal hepatic lobule structure (Figure 8A). In contrast, the liver tissue in Group 2 (IC) displayed significant alterations, including fibroplasia in the portal triad (Figure 8D), mononuclear cell infiltration associated with focal hepatocellular necrosis (Figure 8C), and portal infiltration with mononuclear cells (Figure 8E). These findings indicate that CPM administration in Group 2 (IC) has severely damaged the tissue by increasing toxicity levels. However, no histological changes were observed in the liver tissues in Group 3 (GA1) and Group 4 (GA2) (Figures 8F and 9A). Yet, examining certain sections from Group 5 (GA1+IC)a demonstrated improvement as they showed only slight activation of Kupffer cells (Figure 9D). These sections also showed small focal hepatocellular necrosis associated with mononuclear cells infiltration (Figure 9B) and apoptosis of hepatocytes associated with infiltration of mononuclear cells (Figure 9C). Furthermore, the liver tissue in Group 6 (GA2+IC) showed improved histological features in comparison with Group 2 (IC). Liver tissues did not exhibit any histological changes (as depicted in Figure 10A) except a minor Kupffer cell activation and hepatoportal blood channel congestion shown in Figure 10C. The liver tissue in Group 7 (GA1+IC)b exhibited a regression of histological abnormalities, similar to Group 6 (GA2+IC), except for a minor activation of Kupffer cells in the evaluated sections (Figures 10D, E, and F). In this histological examination, the groups that received GA treatment showed repairing effects in their liver tissue, suggesting that the antioxidant effect imposed by GA elevates antioxidant levels, thereby reducing the oxidative stress caused by CPM administration. Consequently, liver function parameters such as ALT, AST, Total Bilirubin, and ALP were improved.

Histopathological examination of kidney tissue

The normal histological structure of the renal parenchyma was revealed by the histopathological examination of kidney tissue in Group 1 (NC) (Figures 11A and B). However, the kidney tissue in Group 2 (IC) displayed severe damage, as evidenced by periglomerular fibroblast proliferation (Figure 11D), thickening of the glomerular basement membrane (Figure 11E), and interstitial inflammatory cell infiltration, and vacuolization of the renal tubular epithelium (Figure 11F). Additionally, localized necrosis of the renal tubules linked to inflammatory cell infiltration was observed (Figure 11C). On the other hand, no histological changes were seen in kidney tissue in Group 3 (GA1) and Group 4 (GA2) (Figures 12A, B, C, and D). However, the kidney tissue in Group 5 (GA1+IC)a showed improvement in comparison with Group 2 (IC), with sections displaying renal tubular epithelium with granular or vacuolar degeneration, congested glomerular tufts, and congested renal blood vessels (Figures 11E and F). Sections in Group 6 (GA2+IC) similarly showed renal tubular epithelial vacuolar degeneration and glomerular tuft congestion (Figures 13A, and B). Similarly, the kidney tissue in Group 7 (GA1+IC)b showed notable regressive lesions with no other significant histological changes observed in the evaluated sections (Figures 13C and D). The kidney tissues in this examination showed repairing effects as a result of GA administration. The oxidative stress induced by CPM administration was countered by elevating antioxidant levels which, in turn, improved kidney tissue cells and reduced urea and creatinine levels.
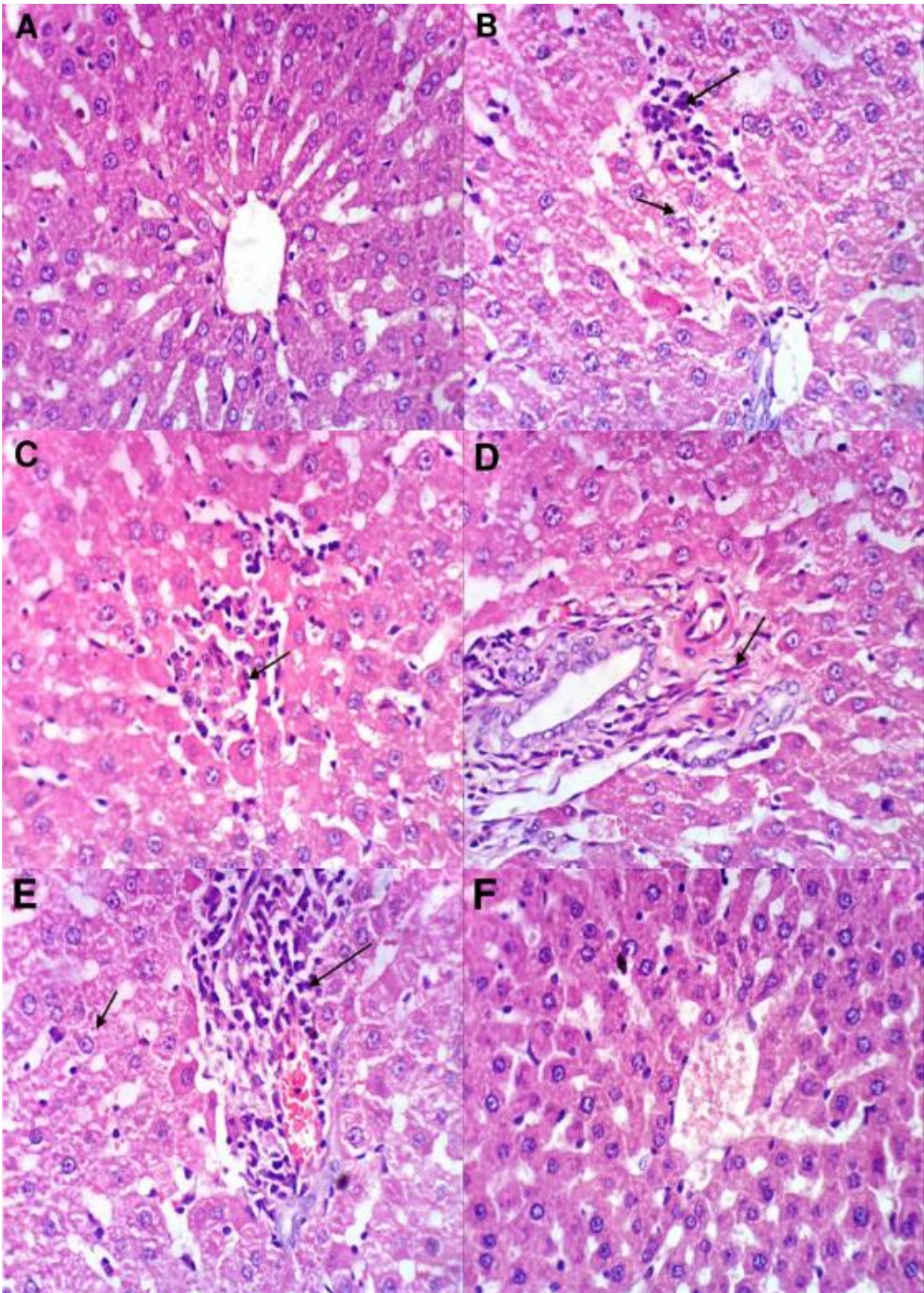
Figure 8. The histopathological changes in liver tissue of rats from group 1, group 2, and group 3 (H&E X 400).

A: Group 1 (NC) showing the normal histological structure of hepatic lobule, **B**: Group 2 (IC) showing cytoplasmic vacuolation of hepatocytes and focal hepatocellular necrosis associated with mononuclear cells infiltration (arrow indicated), C: Group 2 (IC) showing focal hepatocellular necrosis associated with mononuclear cells infiltration in a different area of the tissue (arrow indicated), D: Group 2 (IC) showing fibroplasia in the portal triad, E: Group 2 (IC) showing cytoplasmic vacuolation of hepatocytes and portal infiltration with mononuclear cells infiltration caused by CPM administration (arrow indicated), F: Group 3 (GA1) showing no histopathological alterations, Group 1 (NC): Control group, Group 2 (IC): Rats which administered CPM (3129 mg/kg) daily for 8 weeks, Group 3 (GA1): Rats which received normal GA feed 1 gm/kg body weight daily for 8 weeks.
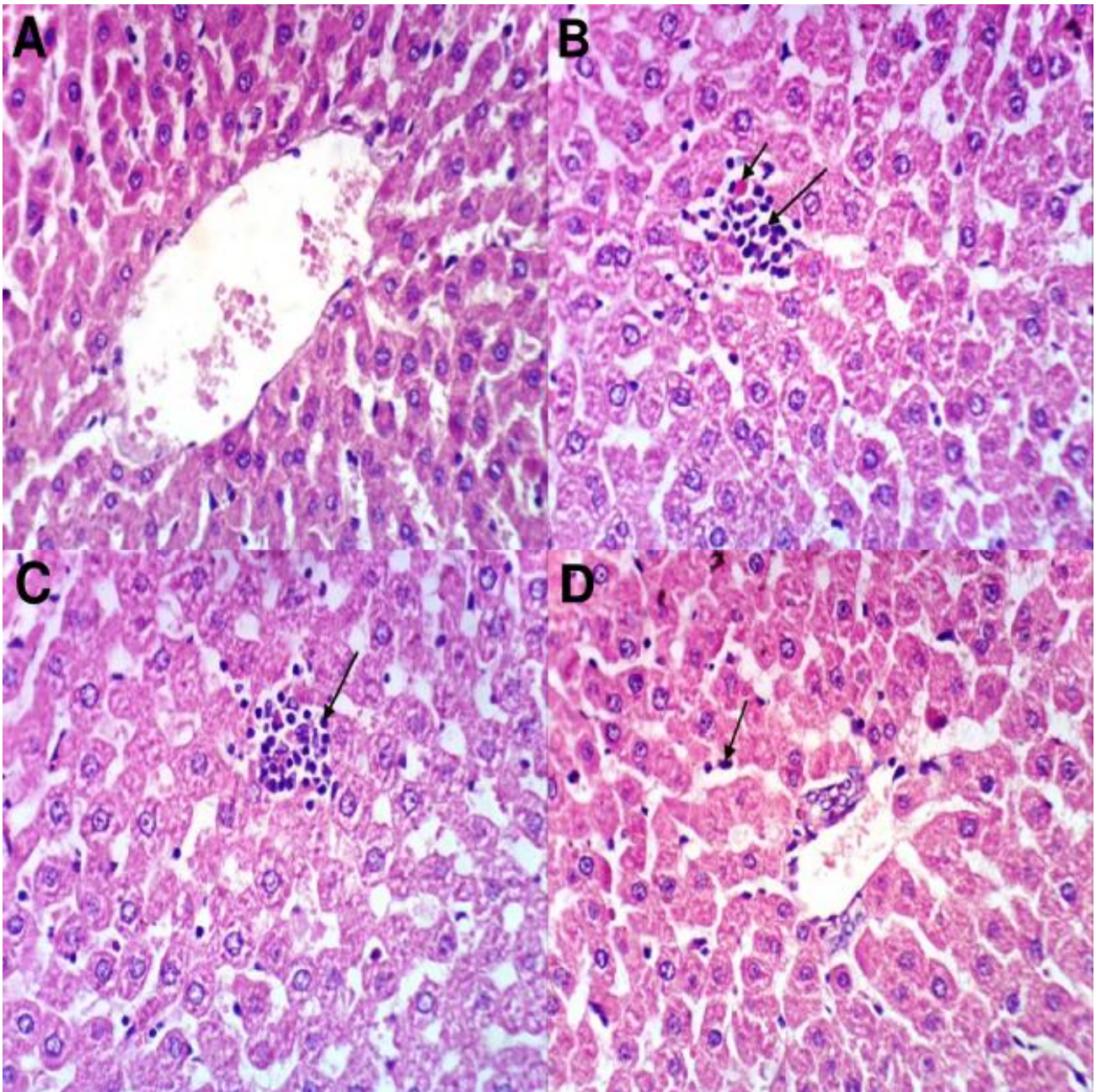
Figure 9. The histopathological changes in rat's liver tissue from group 4, and group 5 (H&E X 400).

A: Group 4 (GA2) showing no histopathological alterations, B: Group 5 (GA1+IC)a showing apoptosis of hepatocytes associated with mononuclear cells infiltration (arrow indicated), C: Group 5 (GA1+IC)a showing small focal hepatocellular necrosis associated with mononuclear cells infiltration (arrow indicated), D: Group 5 (GA1+IC)a showing slight Kupffer cells activation (arrow indicated), Group 4 (GA2): Rats which administered GA 15% w/v in drinking water daily for 8 weeks, Group 5 (GA1+IC)a: Rats which received normal feed and CPM (3129 mg/kg) plus GA (1 gm/kg body weight) daily for 8 weeks.
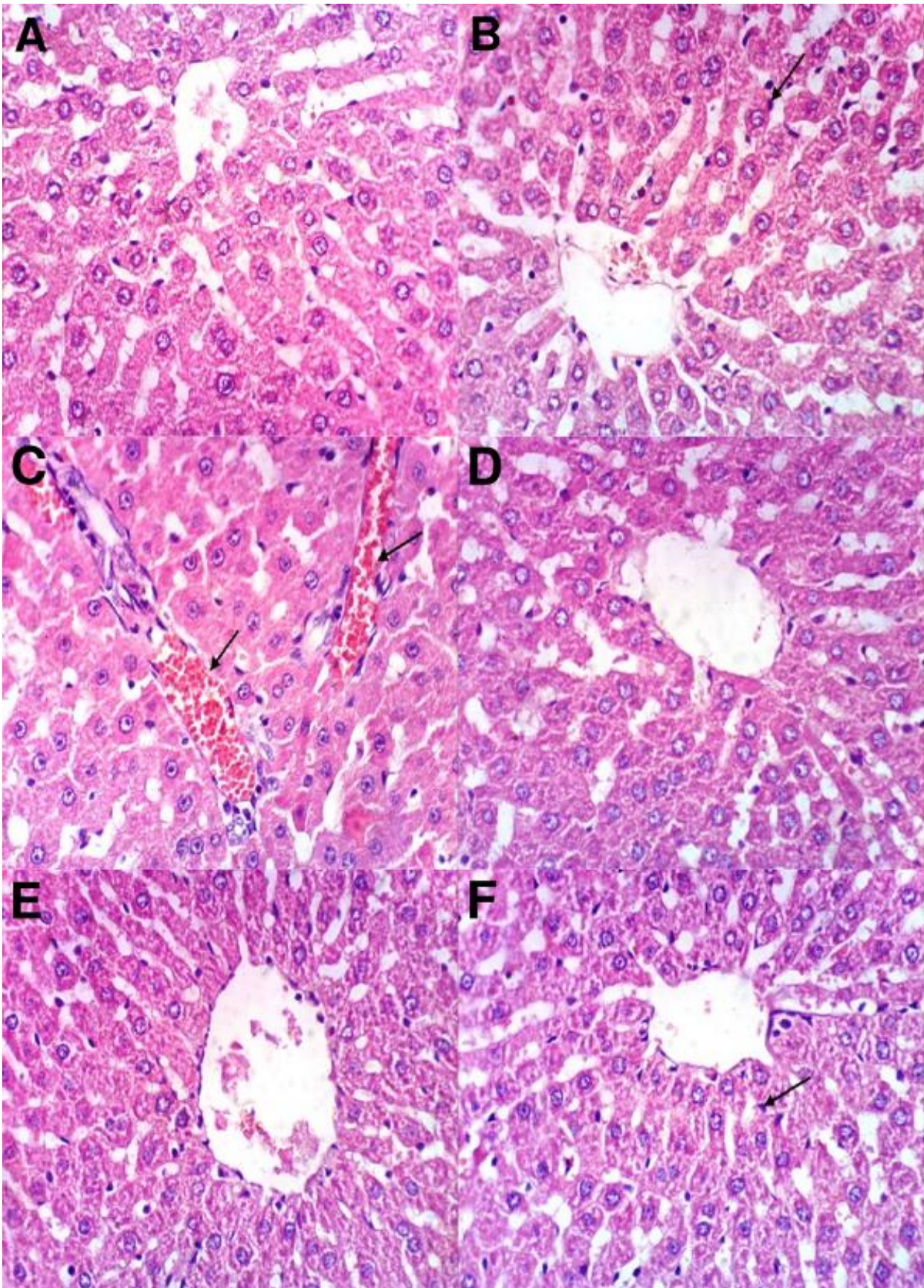
Figure 10. The histopathological changes in rats' liver tissue from group 6, and group 7 (H&E X 400).
A: Group 6 (GA2+IC) showing no histopathological alterations, B: Group 6 (GA2+IC) showing slight Kupffer cells activation (arrow indicated), C: Group 6 (GA2+IC) showing congestion of hepatoportal blood vessels (arrow indicated), D: Group 7 (GA1+IC)b showing no histopathological alterations, E: Group 7 (GA1+IC)b showing no tissue damage, F: Group 7 (GA1+IC)b showing slight Kupffer cells activation (arrow indicated), Group 6 (GA2+IC): Rats which received normal feed and CPM (3129 mg/kg) plus GA 15% w/v in drinking water daily for 8 weeks, Group 7 (GA1+IC)b: Rats which received normal feed plus CPM for 4 weeks, then treated with GA (1 gm/kg body weight) for 4 weeks.
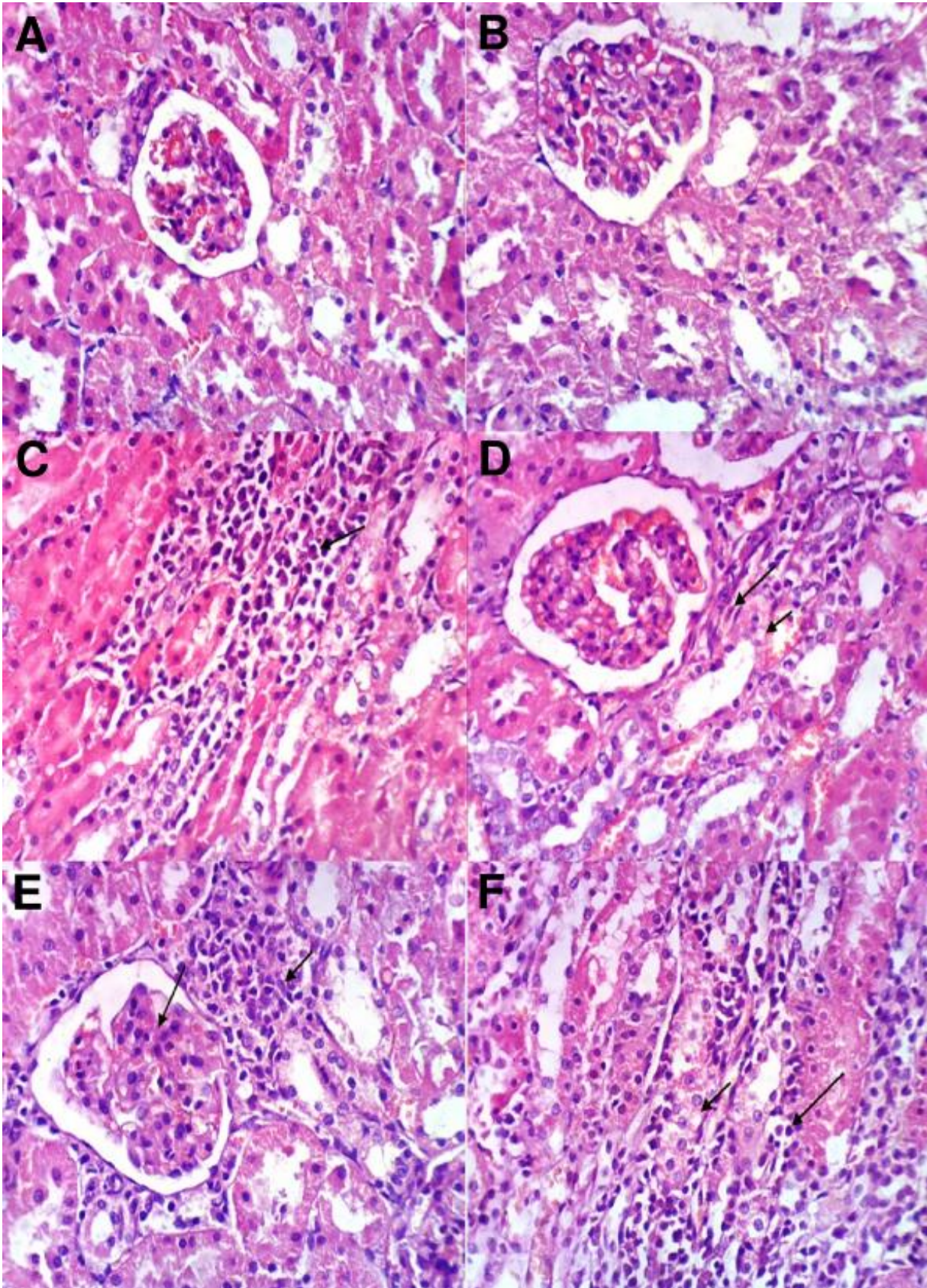
Figure 11. The histopathological changes in rats' kidney tissue from group 1, and group 2 (H&E X 400).
A: Group 1 (NC) showing the normal histological structure of renal parenchyma, B: Group 1 (NC) showing the normal histological structure of renal tissue, C: Group 2 (IC) showing focal necrosis of renal tubules associated with inflammatory cells infiltration (arrow indicated), D: Group 2 (IC) showing vacuolation of renal tubular epithelium and periglomerular fibroblasts proliferation (arrow indicated), E: Group 2 (IC) showing focal necrosis of renal tubules associated with inflammatory cells infiltration and thickening of the glomerular basement membrane (arrow indicated), F: Group 2 (IC) showing vacuolization of renal tubular epithelium and interstitial inflammatory cells infiltration (arrow indicated), Group 1 (NC): Control group, Group 2 (IC): Rats which administered CPM (3129 mg/kg) daily for 8 weeks.
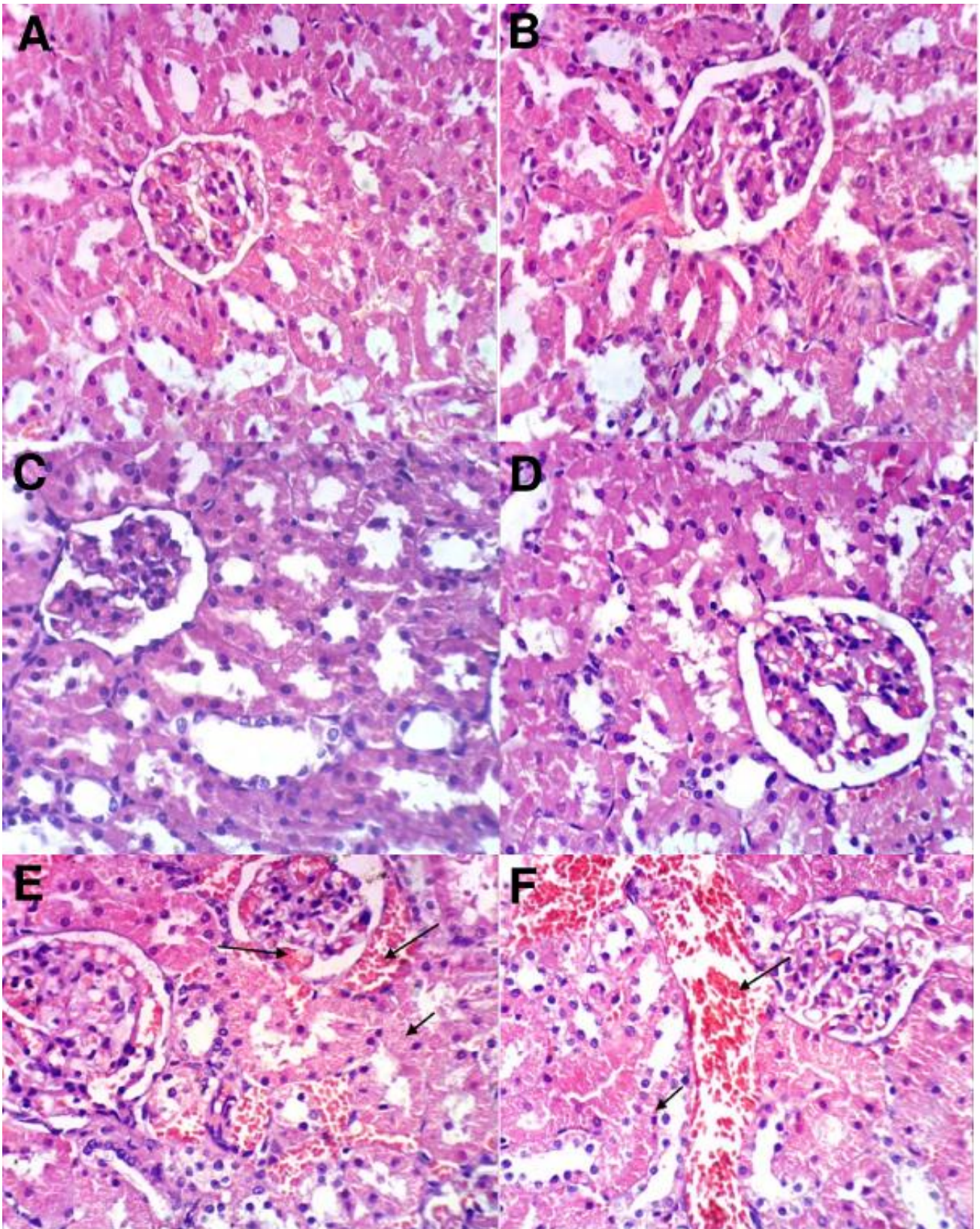
Figure 12. The histopathological changes in rats' kidney tissue from group 3, group 4, and group 5 (H&E X 400).
A: Group 3 (GA1) showing no histopathological alterations, B: Group 3 (GA1) showing also with no tissue damage, C: Group 4 (GA2) showing no histopathological alterations, D: Group 4 (GA₂) showing no histopathological alterations in different area in the tissue, E: Group 5 (GA1+IC)a showing granular degeneration of renal tubular epithelium with congestion of glomerular tufts and renal blood vessels (arrow indicated), F: Group 5 (GA1+IC)a showing granular degeneration of renal tubular epithelium and congestion of renal blood vessels indicating damage done by CPM treatment (arrow indicated), Group 3 (GA1): Rats which received normal GA feed 1 gm/kg body weight daily for 8 weeks, Group 4 (GA2): Rats which administered GA 15% w/v in drinking water daily for 8 weeks, Group 5 (GA1+IC)a: Rats which received normal feed and CPM (3129 mg/kg) plus GA (1 gm/kg body weight) daily for 8 weeks.
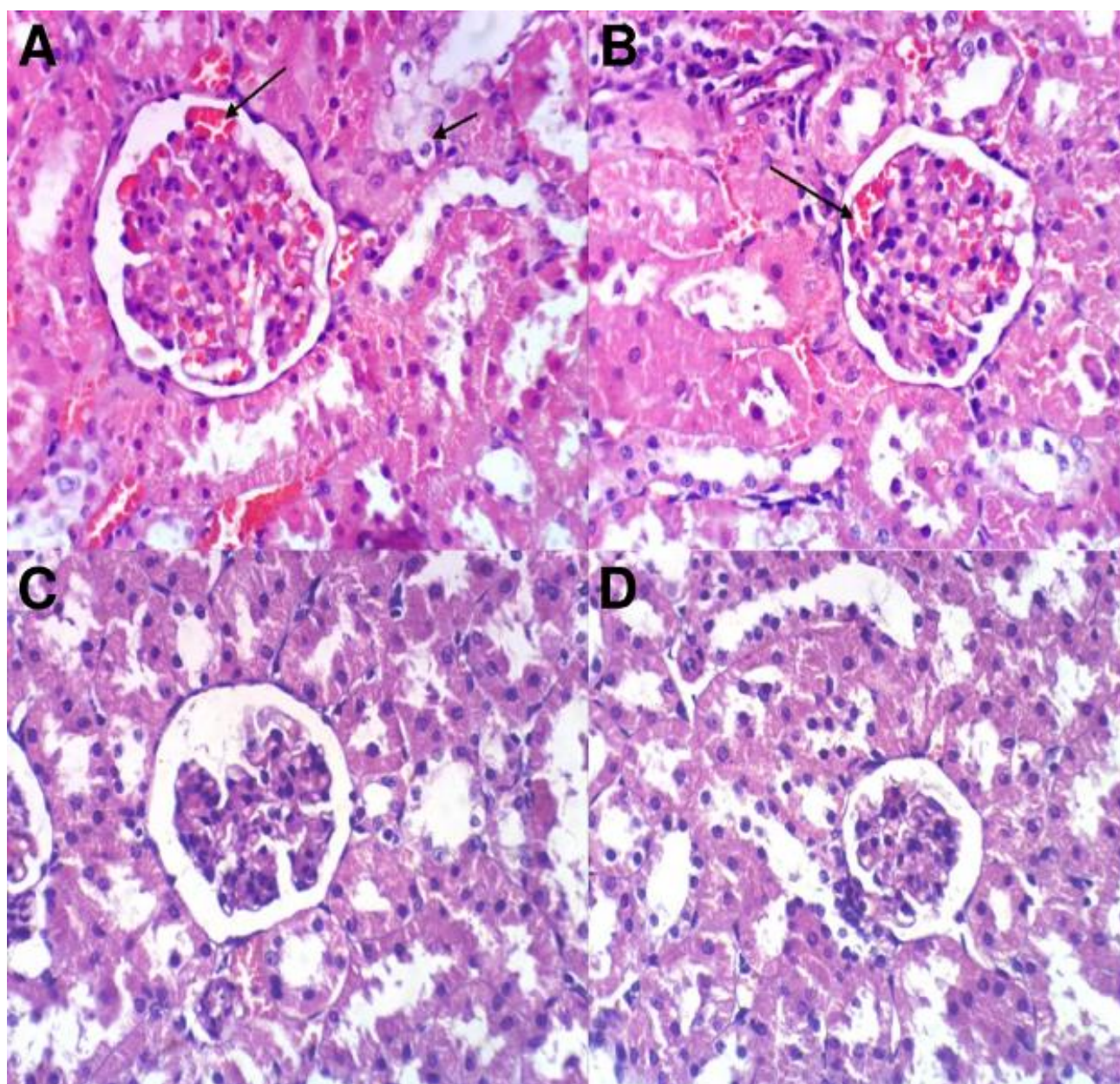
Figure 13. The histopathological changes in rats' kidney tissue from group 6, and group 7 (H&E X 400).

A: Group 6 (GA2+IC) showing vacuolar degeneration of renal tubular epithelium and congestion of glomerular tufts (arrow indicated), B: Group 6 (GA2+IC) showing congestion of glomerular tufts, C and D: Group 7 (GA1+IC)b showing no histopathological alterations (arrow indicated), Group 6 (GA2+IC): Rats which received normal feed and CPM (3129 mg/kg) plus GA 15% w/v in drinking water daily for 8 weeks, Group 7 (GA1+IC)b: Rats which received normal feed plus CPM for 4 weeks, then treated with GA (1 gm/kg body weight) for 4 weeks.

DISCUSSION

As more zones with high CKD risk are identified among agricultural, the focus on environmental exposures as causes of kidney disease is expanding. Since agricultural laborers are more likely to develop CKD, research on agriculture with special attention on herbicides and insecticides has increased (Tejchman et al., 2021). Acute kidney damage has been associated with specific agents; nevertheless, chronic exposure to industrial pollutants and agrichemicals can cause CKD (Prudente et al., 2021). Another possible cause of kidney illness is occupational exposure to infectious agents such as insecticides (Twombley et al., 2011). Hepatic damage, which can eventually result in liver cirrhosis, and renal dysfunction, which can progress to CKD, end-stage renal disease, or cardiovascular disease, can be avoided by using natural products such as GA for nephron and hepatic protection (Kamal et al., 2021). GA contains antioxidant macromolecules, including lysine, tyrosine, and histidine, which enhance its antioxidant activity (Naiel et al., 2021). It has been shown to lower urea nitrogen and creatinine levels, thus improving renal function in patients with diabetic nephropathy (Alshelleh et al., 2023). Additionally, GA significantly reduces fasting blood glucose, HbAc1 levels, blood

uric acid, and total protein levels. Moreover, it facilitates the passage of minerals and water from the intestinal lumen into the circulation (Salama et al., 2021).

One of the several health benefits of GA is its renal protection; it is believed that the main mechanism is GA's ability to increase nitrogen excretion, which lowers serum urea nitrogen levels (Alshelleh et al., 2023). GA is also recognized as a rich source of K^+, Mg^{2+}, and Ca^{2+} dietary fiber (Prasad et al., 2022). Furthermore, GA enhances creatinine clearance in healthy mice and promotes the excretion of antidiuretic hormone (ADH) and Ca2+ in the kidneys and intestines (Farman et al., 2020). One of the key advantages of GA is its role in increasing nitrogen excretion in stool, thereby reducing serum urea nitrogen levels. This occurs because the bacterial flora in the large intestine slowly ferments GA to form short-chain fatty acids (Salama et al., 2021). Additionally, GA can raise the quantity of lactic acid bacteria and Bifidus in healthy individuals (Yousefi et al., 2023). A previous study found that rats consuming 25–30 g of GA daily for 21-30 days experienced a reduction in total cholesterol by 6% and 10.4%, respectively. There was no impact on HDL or triglycerides; the reduction was restricted to LDL and VLDL, which aligns with the present results (Sharma, 1985).

GA has been used as a dental hygiene agent; after GA therapy, the gingival and plaque index scores were dramatically reduced when an herbal mixture containing GA was applied directly to the teeth and gums (Al-Jubori et al., 2023). The present study found that GA treatment at different doses in drinking water had beneficial hepatic and renal effects. After four weeks of treatment, improvements in kidney and liver function parameters were observed, along with enhanced measurements of antioxidant enzymes. GA treatment effectively mitigated the negative effects of CMP administration on most of kidney and liver parameters.

In terms of kidney tests, the study found that administering GA at doses of 1 g/kg body weight and a 15% weight/volume solution in drinking water for eight weeks resulted in a considerable reduction in urea and creatinine levels, consistent with Tichati et al. (2020). The increase in ALT level by GA administration in Group 3 (GA1) at 1g/kg body weight rate is in accordance with Fareed et al. (2022). However, unlike the present findings, another study reported that 0.5 g/kg b.wt/rat/day GA for 45 days increased AST and alkaline phosphatase levels (Kamal et al., 2021). A study employing a 3% GA solution for six days at a 100 mg/kg body weight dose indicated that low dosages (100 and 500 mg/day) were associated with high levels of AST and ALP, while higher doses (10 grams, 10%, and 15% daily) led to lower levels of these parameters (Babiker et al., 2017). These findings suggest that the efficacy of GA on liver function is dosage-dependent concerning alterations in lipid profile (Al-Jubori et al., 2023). Similar to the findings of El-Deeb et al. (2007), the present data demonstrated significant increases in total cholesterol, triglycerides, LDL, and VLDL, along with a significant reduction in HDL with CPM administration (3129 mg/kg) compared to the NC Group 1. In terms of antioxidant parameters, Group 2 (IC) showed a considerable decrease in antioxidant enzymes (free radical scavengers) and a significant increase in lipid peroxidation. However, the current study discovered that catalase, reduced glutathione (GSH), and superoxide dismutase (SOD) had a strong antioxidant activity, which GA markedly increased, while it decreased malondialdehyde (MDA) levels. These findings are similar to those reported by Ahmed et al. (2022).

Colon cancer results from oxidative stress caused by 1, 2-dimethylhydrazine (DMH), which damages DNA in animals' colon cells, liver, kidneys, heart, stomach, and lungs (Jelic et al., 2021). This will, in turn, result in an insufficient immune response, increased oxidative damage to lipids and proteins, lung metastasis, and the formation of alkylated DNA adducts in kidneys. Gum Arabic (GA) and Eugenol (EUG), administered either alone or combined, effectively prevent and cure rat kidney tissue and spleen geno-toxicity (Dutra et al., 2022). According to a study, rats with colorectal carcinogenesis exhibited a synergistic effect of GA and EUG on genotoxicity in the spleen and kidney tissues (Melo et al., 2023).

Histopathological results in the present study showed the anti-inflammatory and antioxidant effects of GA by reversing histopathological changes such as inflammatory cell infiltration, necrosis, apoptosis, and fibroplasia caused by oxidative stress in liver and kidney tissues. These findings align with the results of Ayaz et al. (2017).

CONCLUSION

The cytotoxic effects of chlorpyrifos-methyl, which cause oxidative stress and inflammation in liver and kidney tissues, were found to be significantly reduced by GA's strong antioxidant ability. The histological analysis of GA revealed enhanced efficacy on both liver and kidney tissues, as well as improvements in antioxidants such as Catalase, GSH, SOD, and MDA in the treated groups. Ultimately, GA (1 g/kg) demonstrated its ability to protect renal and hepatic organs against oxidative stress induced by chlorpyrifos-methyl (3129 mg/kg) administration. Future studies should evaluate the targeted genes affected by oxidative stress due to chlopyrifos-methyl administration, assess the reparative effects of GA as an antioxidant on those genes. and show how its antioxidant properties contribute to physiological mechanisms in liver and kidney tissues.

DECLARATIONS

Authors' contributions

The study design and experiment scheduling were contributed by Professors Hanaa Fawzy and Yasmin Emam, while the data analysis was done by Professor Emam Abd Al-Mobdy. All authors reviewed the analyzed data and gave their approval to the final draft of the manuscript.

Ethical considerations

The authors confirm that all authors have reviewed and submitted the manuscript to this journal for the first time. Additionally, all authors checked the originality of data and sentences via plagiarism checkers.

Availability of data and materials

The original data presented in the study are included in the article. For inquiries, please contact the corresponding author/s.

Conflict of interests

No conflicts of interest have been disclosed by the authors.

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