Original article

Sub-chronic toxic effects of gibberellic acid on liver and kidney of adult albino rats: role of oxidative stress

Amani Abd El Fattah Bayoumy[1], Mervat Hamdy Abd El Salam[1], Abla Abd El Rahman Ali[1], Randa Mohey El Din El Shenawy[1], Olfat Abd El Latif Sayed Radwan[2], Mai Moustafa Magdi[1]*

[1]Forensic and Clinical Toxicology department, faculty of medicine, Cairo university. [2]Toxicology - Pesticides Analysis Department, Central Agricultural Pesticide Lab (CAPL)

***Corresponding author**
Mai Moustafa Magdi, M.D.
E mail
Dr.maimagdi_83@kasralainy.edu.eg

ABSTRACT

Introduction: Gibberellic acid (GA3) plays important roles in many cellular processes including promoting stem elongation, and mobilization of food reserves in grass seed germination, juvenility, and sex expression. **The aim of the work:** To detect the possible toxic effects of GA3 on liver and kidney histopathology and effect on indicators of oxidative stress levels. **Material and Methods:** Seventy-five rats were included in the study and divided into two groups of animals (50 rats in treatment group and 25 rats in recovery group). The first group (treatment group) divided into 5 equal subgroups of rats (10 rats each) which were negative control group (G0T) received only distilled water, positive control treatment subgroup (G1T) received diluted sodium hydroxide in distilled water which are vehicle for GA3, subgroup G2T received 1/10 of LD50 (630 mg/kg) of GA3, subgroup G3T received 1/20 LD50 (315 mg/kg) of GA3, and subgroup G4T received 1/40 LD50 (157 mg/kg) of GA3. Treatment groups treated with GA3 orally by gavage for 12 weeks then salvaged by decapitation. The second group (recovery group) containing 25 rats that were treated with same manner as treatment groups for 12 weeks then kept after the treatment for recovery period for 2 weeks then salvaged to detect its cumulative effect. Recovery group divided into 5 equal subgroups (5 rats in each group) which were negative control recovery group (G0R), positive control recovery subgroup (G1R), subgroup G2R, subgroup G3R, and subgroup G4T. In all subgroups, liver and kidney tissue samples were taken to measure level of hepatic MDA concentration, hepatic catalase activity and examine hepatic and renal histopathologic changes. Results: hepatic MDA was significantly increased in all treatment and recovery groups in comparison to both control groups and level was directly proportional to dose of GA3 administered. There was significant reduction in the hepatic catalase enzyme activity in all treatment groups than the control treatment group especially in the group of highest doses (G2T). After the recovery period, the hepatic catalase enzyme activity continued to drop than its level after the treatment period, especially in the group (G2R). Histopathological examination revealed marked necrosis of tissues of, and the recovery period couldn't restore these pathological changes due to the cumulative effects of GA3 on the liver and kidneys. **Conclusion and recommendation**: GA3 possess risk to human health due to oxidative damage to tissues such as liver and kidney. Use of GA3 should be cautious, and its level in agricultural products should be regularly controlled.

Keywords: Gibberellic acid, liver, kidney, Oxidative stress.

I. INTRODUCTION

Plant hormones (phyto-hormones) are defined as small-chemical compounds that are used to promote development of grains (Sonkar et al. 2021). Gibberellins which are one type of plant hormones were first discovered in 1930s as a byproduct of a fungus and were responsible for significant plant elongation. Recent research has shown that gibberellins participate in additional processes (such as induction of flowering and seed germination). GA3, one of the gibberellins, increases and improves the yield of a variety of plants by promoting cell division (Sun et al. 2020).

GA3 is resistant for decay and remains active in soil for months. The Environmental Protection Agency (EPA) has determined using it only in low doses (Panda et al. 2022).

People may be exposed to remnants of GA3 in diet derived from many types of fruits and vegetables treated with GA3. Exposure may occur through drinking water (Tawfik, 2015). Occupational exposure may occur through powder inhalation and dermal at workplaces where GA3 is produced or used leading to acute toxicity (Alsemeh et al. 2019).

Despite being widely utilized, GA3's impacts on human health have not been thoroughly investigated. Only a small number of studies have investigated the potential toxicity of plant growth regulators (PGRs), such as GA3, to mammals. Adenocarcinomas in the liver and kidney of mice have been observed to be predisposed by chronic exposure to GA3. Rats' oxidative stress was also shown to rise after 50 days of exposure to 75 ppm GA3 in their drinking water (Khdar et al. 2022).

Due to its function in xenobiotic detoxification, biotransformation, and excretion, the liver is the first organ to be attacked. It is the first organ to be exposed to such risks through portal circulation after GIT absorbs hazardous compounds. Rat liver histopathology is significantly altered by GA3.Among the pathological symptoms observed was the significant leucocytic infiltrations in the liver of GA3-treated animals. These leucocytic infiltrations caused by immune response of any tissue exposed to injurious chemical (Alsemeh et al. 2019).

The kidney is very vulnerable to chemical toxicity due to a number of factors, including its high blood flow and complexity on an anatomical and functional level. Most toxins are primarily eliminated by the urine. Toxins are concentrated in the filtrate, moved through the tubular cells by the kidney, and some of them are even bioactivated. The kidneys are highly susceptible to a number of disorders as a result of all these functions (Husseiny et al, 2020). Interstitial fibrosis and tubular atrophy are two renal tubule disorders (increased with progressive glomerular damage and loss). (Rahm et al. 2017).

According to Iwan et al. (2021), Plant Growth Regulators (PGRs) induced oxidative stress leading to the generation of free radicals and caused lipid peroxidation.

Plant growth regulators (PGRs) cause oxidative stress that cause free radicals' generation and lipid peroxidation, some enzymes are affected such as catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidases (GPx) (Hussein et al. 2015).

II. AIM OF THE WORK:

The aim of the present work was to detect the possible toxic effects of GA3 on liver and kidney of adult male albino rats and assess the role of oxidative stress.

III. MATERIAL & METHODS:

1. Test Materials:

Plant growth regulator: GA3

- **Trade name**: gibberellin 20%
- **Type of formulation**: powder form
- **Name of formulation:** "Berelex" 20% active ingredient of GA3 which obtained from Syngenta-Switzerland Company
- **Dissolvent:** Sodium Hydroxide in distilled water

2. Animals & Experimental Design:

In the current study, 75 mature male albino rats were employed. They were bought from the faculty's animal shelter at Cairo University's Faculty of Medicine. The animals were raised in the proper settings for two weeks at the animal home of "The Central Agricultural Pesticide Laboratory (CAPL)" in Cairo, Egypt, to adapt before treatments. They were given a conventional laboratory food and free access to water. The typical diet consists of 21% protein and 3% fat. Fibers: 4% 3. 10% carbohydrate in a 3% concentration.

Rats were divided into two groups of animals (50 rats in treatment group and 25 rats in recovery group).

- **The first group** (treatment group) divided into 4 equal subgroup of rats (10 rats each) which were:
    1. Negative control treatment subgroup (G0T) received only distilled water.
    2. Positive control treatment subgroup (G1T) received diluted sodium hydroxide in distilled water which are vehicle for GA3.
    3. Subgroup G2T received 1/10 of LD50 (630 mg/kg) of GA3.
    4. Subgroup G3T received 1/20 LD50 (315 mg/kg) of GA3.
    5. Subgroup G4T received 1/40 LD50 (157 mg/kg) of GA3.
    - Treatment groups treated with GA3 orally by gavage for 12 weeks then salvaged by decapitation.
- **The second group** (recovery group) containing 25 rats that were treated with same manner as treatment groups for 12 weeks then kept after the treatment for recovery period for 2 weeks then salvaged by decapitation to detect its cumulative effect. Recovery group divided into 5 equal subgroups (5 rats in each group) which were:
    1. Negative control recovery subgroup (G0R).
    2. Positive control recovery subgroup (G1R)
    3. Subgroup G2R (after 12 weeks treatment with 1/10 LD50 of GA3)
    4. Subgroup G3R (after 12 weeks treatment with 1/20 LD50 of GA3)
    5. Subgroup G4T (after 12 weeks treatment with 1/40 LD50 of GA3)
- LD50 for GA3 was 6300 mg/kg body weight (Material Safety Data Sheet. Gibberellic acid,2012).
- Treatment groups (G2T, G3T, and G4T) were statistically compared with positive control treatment group (G1T).
- Recovery groups (G2R, G3R, and G4R) were statistically compared with positive control recovery group (G1R).
- The rats of each group were weighed at the beginning of the experiment then every week for 12 weeks, the change in body weight was calculated and recorded to adjust the dose.

Methods:

1-Biochemical study:

Assessment of tissue oxidative stress markers:

Each **liver specimen** was divided into 2 parts,

i. **ure**aluminum foil and embedded in liquid nitrogen for 1 hour then kept frozen in -80°C till used to assess MDA level and catalase enzyme activity. Assessment of MDA level was done as described by **Khoubnasabjafari et al. (2015)** following steps mentioned in the pamphlet of Bio diagnostic kits using calorimetric method. While assessment of catalase enzyme activity was done according to **Soliman et al. (2010).**

ii. **The 2nd parts were preserved for Histopathological examination.**

2- Histologic Study:

For light microscopic study, liver and kidney specimens were fixed in 10% formalin saline for histo-pathological examination using H&E stain by following the method described by **Melo et al. (2020) and (Husseiny et al, 2020).**

Liver histopathologic changes were scored using the scoring system according to **Kleiner et al. (2005).**

kidney histopathologic changes were scored using the scoring system according to **Srivastava et al. (2018)**.

3- Statistical analysis:

Data were represented as means ± SD. The differences were compared for statistical significance by ANOVA and student's t-test. Difference was considered significant at $p < 0.05$. The statistical analysis was performed using SPSS software (SPSS, version 25, PSS, Inc., IL, USA) **(Milovanović, & Perišić, 2020)**

IV. RESULTS:

Statistical comparison done between negative and positive control groups regarding the study parameters (hepatic MDA levels, Hepatic catalase changes in both liver and kidney) that revealed no statistical difference (with p value > 0.05), so only results of positive control groups were used for comparison with other subgroups.

- **Effects of GA3 treatment on MDA**

Effects of GA3 on MDA level on orally treated rats are represented in **(Table 1)** and **(Figure1)**. There was significant increase in the hepatic MDA concentration in all groups of GA3 treated rats than the control rats especially in the group of highest doses (G2T) with p-value 0.035.

After the recovery period the MDA level is reduced than its level after the treatment period, but its values are still higher than the control rats especially in the group **(G2R).**

Table (1): Effect of GA3 on hepatic MDA level of rats after 12 weeks and after recovery period for 2 weeks using ANOVA Test.

Groups / parameters	G1T	G1R	G2T	G2R	G3T	G3R	G4T	G4R	P value
MDA	0.41± 0.2	0.58± 0.14	12.68± 1.1	10.56± 1.5	10.93± 0.73	10.08± 0.56	4.37± 1.2	1.38± 0.28	0.03 5 *

Non-significant if p value >0.05 ***= highly significant if p is <0.01

*Significant if p value < 0.05

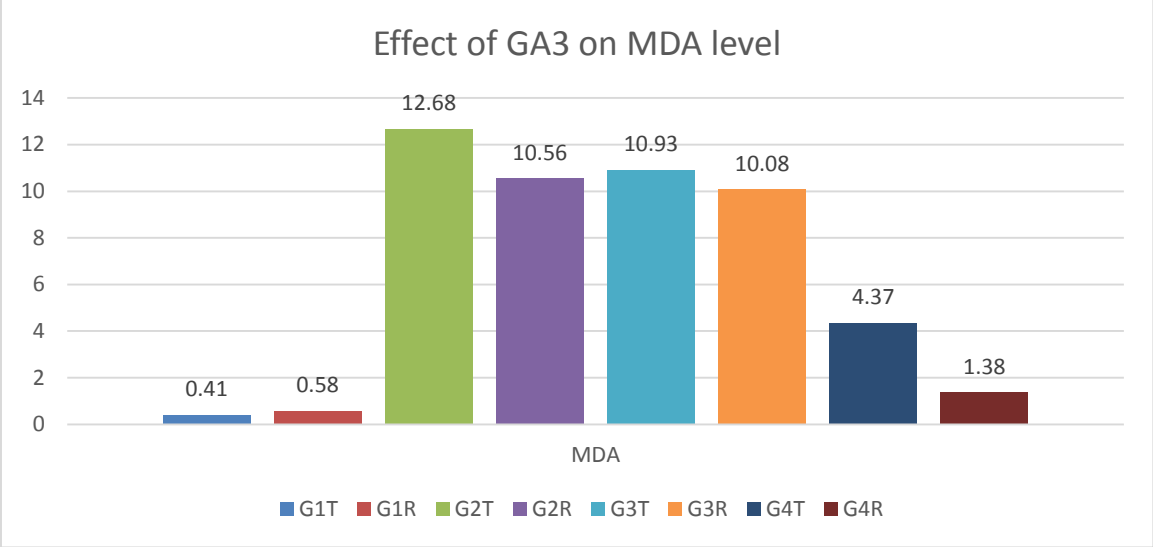

Figure (1): Bar Chart shows the effect of GA3 on hepatic MDA level of rats after 12 weeks and after recovery period for 2 weeks.

The effects of GA3 treatment on hepatic catalase enzyme activity in different study subgroups are illustrated in **(Table 2)** and **(Figure2)**.

There was significant reduction in the hepatic catalase enzyme activity in all treatment groups than the control treatment group especially in the group of highest doses **(G2T)** with p-value 0.028.

After the recovery period, the catalase enzyme activity continued to drop than its level after the treatment period, but its values are still lower than the control rats especially in the group **(G2R).**

Table (2): Effect of GA3 on hepatic catalase enzyme activity of rats after 12 weeks and after recovery period for 2 weeks using ANOVA Test.

Groups / parameters	G1T	G1R	G2T	G2R	G3T	G3R	G4T	G4R	P value
Cat	178.131± 14.672	154.507± 9.347	126.41± 18.937	116.59± 13.086	130.518± 24.098	172.796± 30.976	160.579± 25.485	134.05± 30.16	0.028*

Non-significant if p value >0.05 ***= highly significant if p is <0.01

*Significant if p value < 0.05

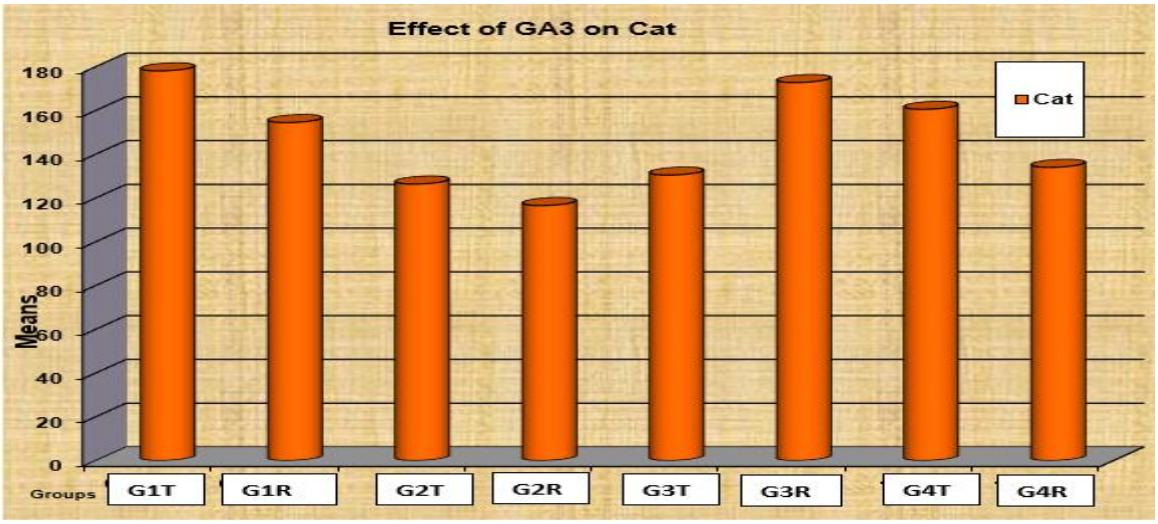

Figure (2): Bar Chart shows the effect of GA3 on hepatic catalase enzyme activity (Cat) of rats after 12 weeks and after recovery period for 2 weeks

Histopathological results

Results of histopathology were demonstrated in **tables (1, 2),** and in **figures (3-6)**

Liver: the control group showed normal liver architecture which consists of central vein and hepatic cords arranged in array matter. There are sinusoids and the portal area, which contains the hepatic artery, portal vein, and bile ducts, in between these cords. Liver lesions in the GA3 treated groups were represented by congestion of the blood vessels, vacuolation of the hepatic cells and necrosis of some cells. These lesions were gradually increased in severity with increase of GA3 doses till reaching to complete necrosis of the hepatic cells with the highest dose (1/10 of LD50 of GA3).

Kidneys: the control group showed normal kidney architecture which consists of glomeruli and renal tubules which are lined by cuboidal cells. Kidneys lesions in the GA3 treated groups revealed vacuolation of the cells lining the renal tubules, congestion of blood vessels, periglomerular edema. Also, necrosis was noticed in certain cells. These lesions were severe in the group G2T, moderate in the group G3T and mild in the group G4T.

Recovery period: the recovery period couldn't restore the pathological lesions, the organs especially the liver and kidney especially in the group with the highest dose (G2R that received 1/10 of LD 50). In groups G3R and G4R some hepatocytes suffered from mitotic division.

Table (1): The score of pathological changes of the liver of different groups

Groups / Pathological changes	G2T	G3T	G4T	G2R	G3R	G4R
Vacuolation of hepatic cells	+++ve	++ve	+ve	++ve	++ve	+ve
Necrosis of hepatic cells	+ve	++ve	+ve	+++ve	++ve	+ve
Congestion of blood vessels	+++ve	++ve	+ve	-ve	-ve	-ve
Hemolysis of blood	-ve	-ve	-ve	++ve	+ve	++ve
Multinucleated giant cells (pri-carcinogenic stages)	-ve	-ve	-ve	-ve	+ve	++ve

+++ve= severe lesion ++ve= moderate lesion +ve lesion= mild lesion -ve lesion= no lesion

Table (2): The score of pathological changes of kidneys of different groups

Groups / Pathological changes	G2T	G3T	G4T	G2R		G3R	G4R
Vacuolation of cells of renal tubules	+++ve	++ve	+ve	+ve		+ve	+ve
Necrosis of cells of renal tubules	+ve	+ve	+ve	++ve		++ve	++ve
Periglomerular edema	+++ve	++ve	+ve	-ve		-ve	-ve
Congestion of blood vessels	+++ve	++ve	+ve	+ve		+ve	+ve

+++ve= severe lesion ++ve= moderate lesion

+ve lesion= mild lesion -ve lesion= no lesion

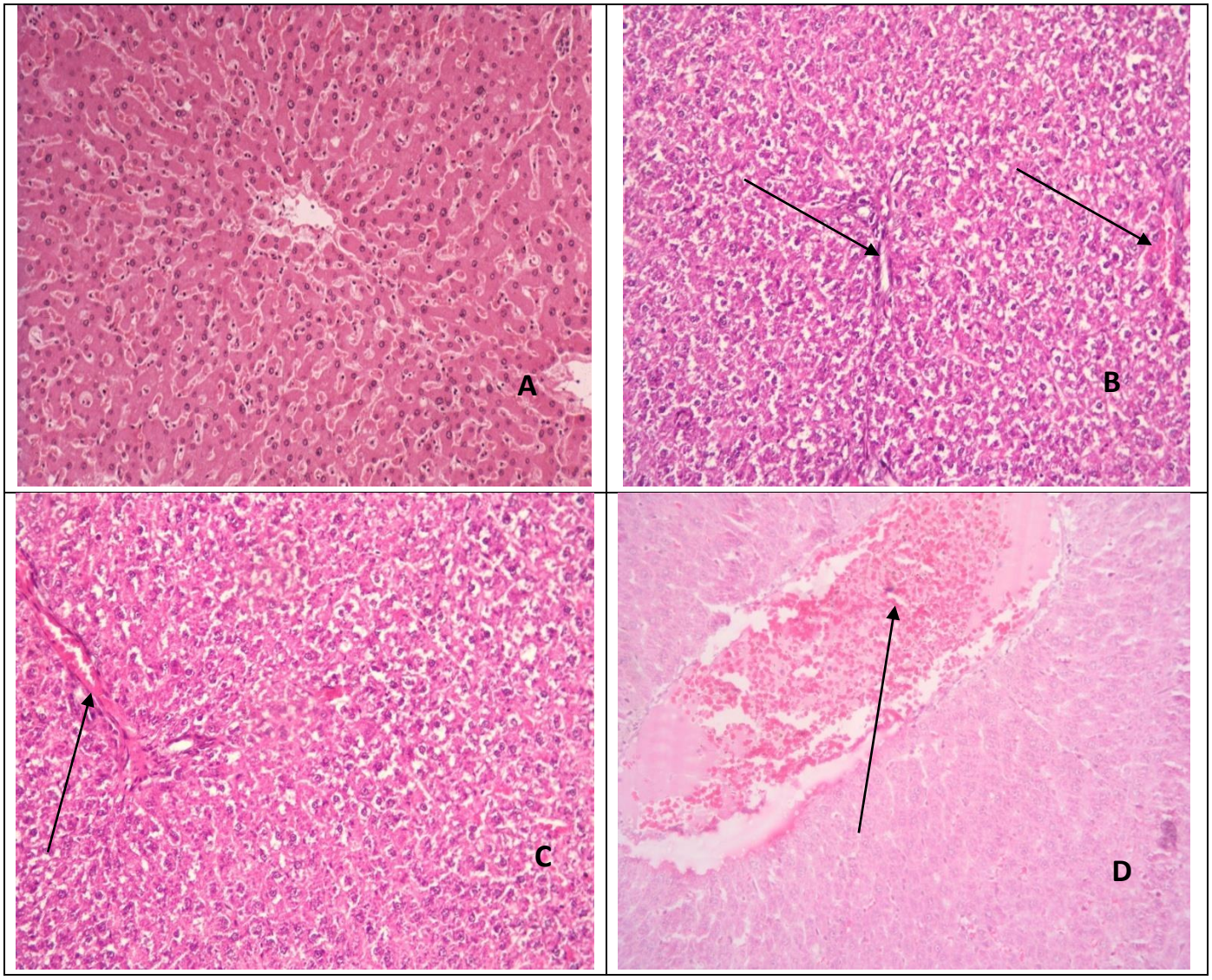

Figure (3): Effects of GA3 on the liver of male albino rats after treatment for 12 weeks.

(A) Control liver: showing normal liver architecture.

(B)Liver of group G2T: showing congested blood vessels in the portal area (arrows). Some hepatocytes suffer from necrobiotic changes.

(C) Liver of group G3T: Congested portal blood vessels (arrow) & vascular degenerative changes of hepatocytes with activation of vankoper cells

(D) Liver of group G4T: some hepatocytes suffered from vacuolar degenerative changes, others showed necrosis (arrow) and severe dilated blood vessels were noticed.

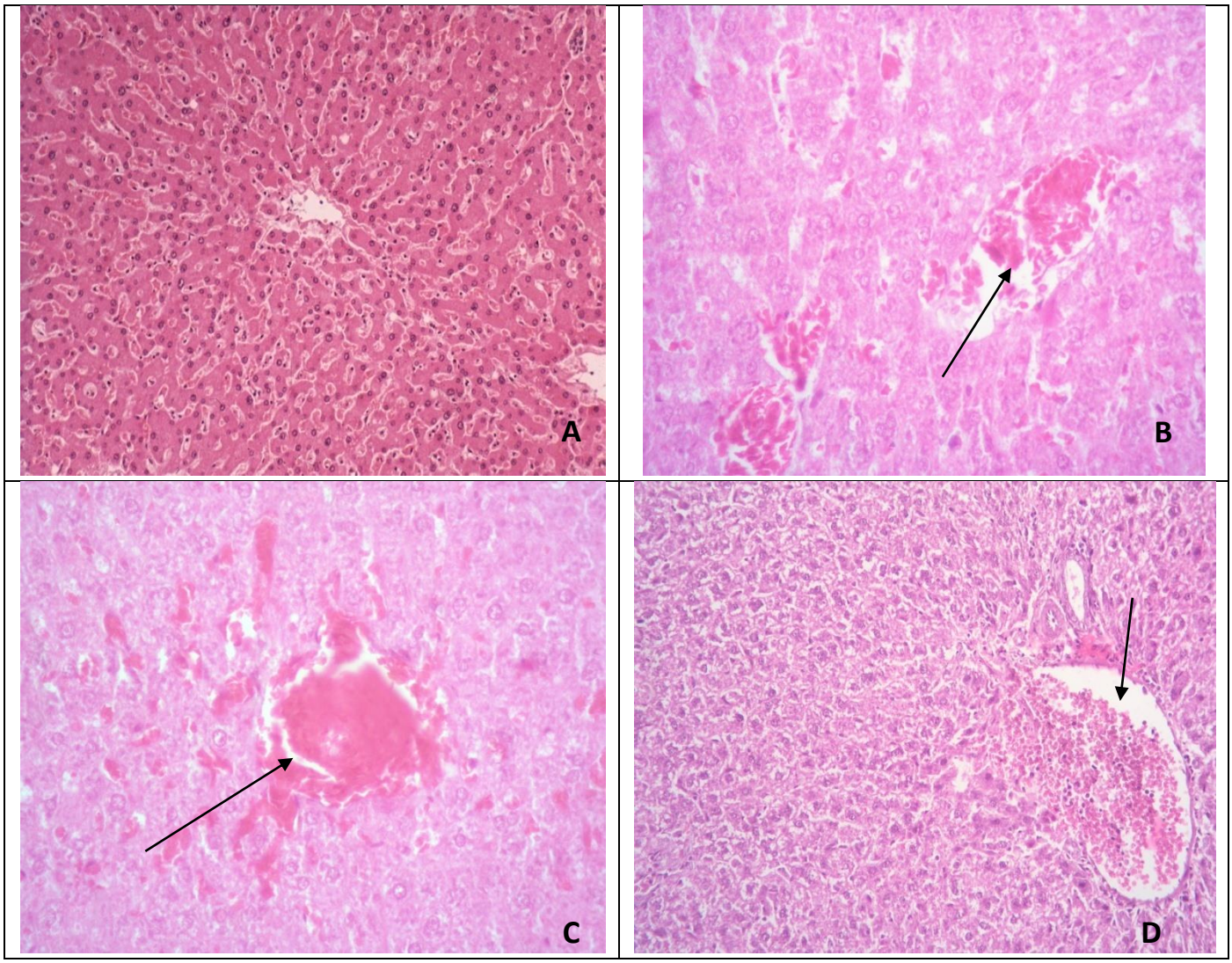

Figure (4): Effects of GA3 on the liver of rats after recovery period (R) for 2 weeks **Control recovery (G1R):** showing normal liver architecture.

(A) Liver of group (G2R): severe dilated & congested blood vessels (arrow) & severe necrosis of hepatocytes were noticed.

(B) Liver of group (G3R): severe necrosis of hepatocytes (arrow) & hemolysis of blood in between.

(C) Liver of group (G4R): Giant multinucleated hepatocytes were also noticed. Severe dilated & congested blood vessels (arrow) & severe necrosis of the hepatocytes were noticed.

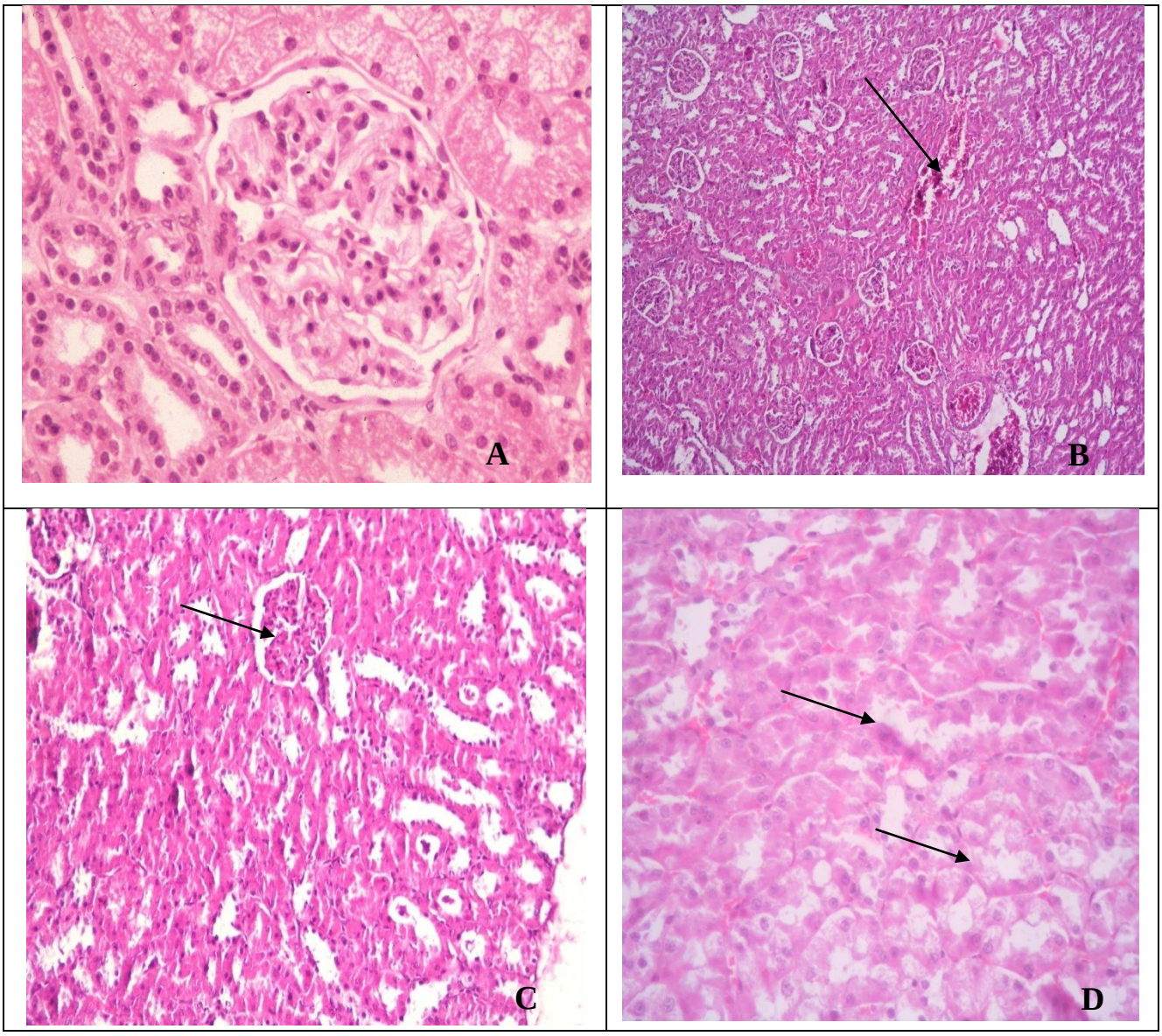

Figure (5): Effects of GA3 treatment on the kidney of rats after treatment for 12 weeks.

(A) Control group (G1T): showing normal kidney architecture.

(B) Kidney of group (G2T): complete necrosis of some cells lining the renal tubules (arrows)

(C) Kidney of group (G3T): necrosis of some cells lining renal tubules (arrow) also formation of renal casts was seen.

(D) Kidney of group (G4T): showing congestion of most of blood vessels (arrow)& necrosis of some cells lining the renal tubules.

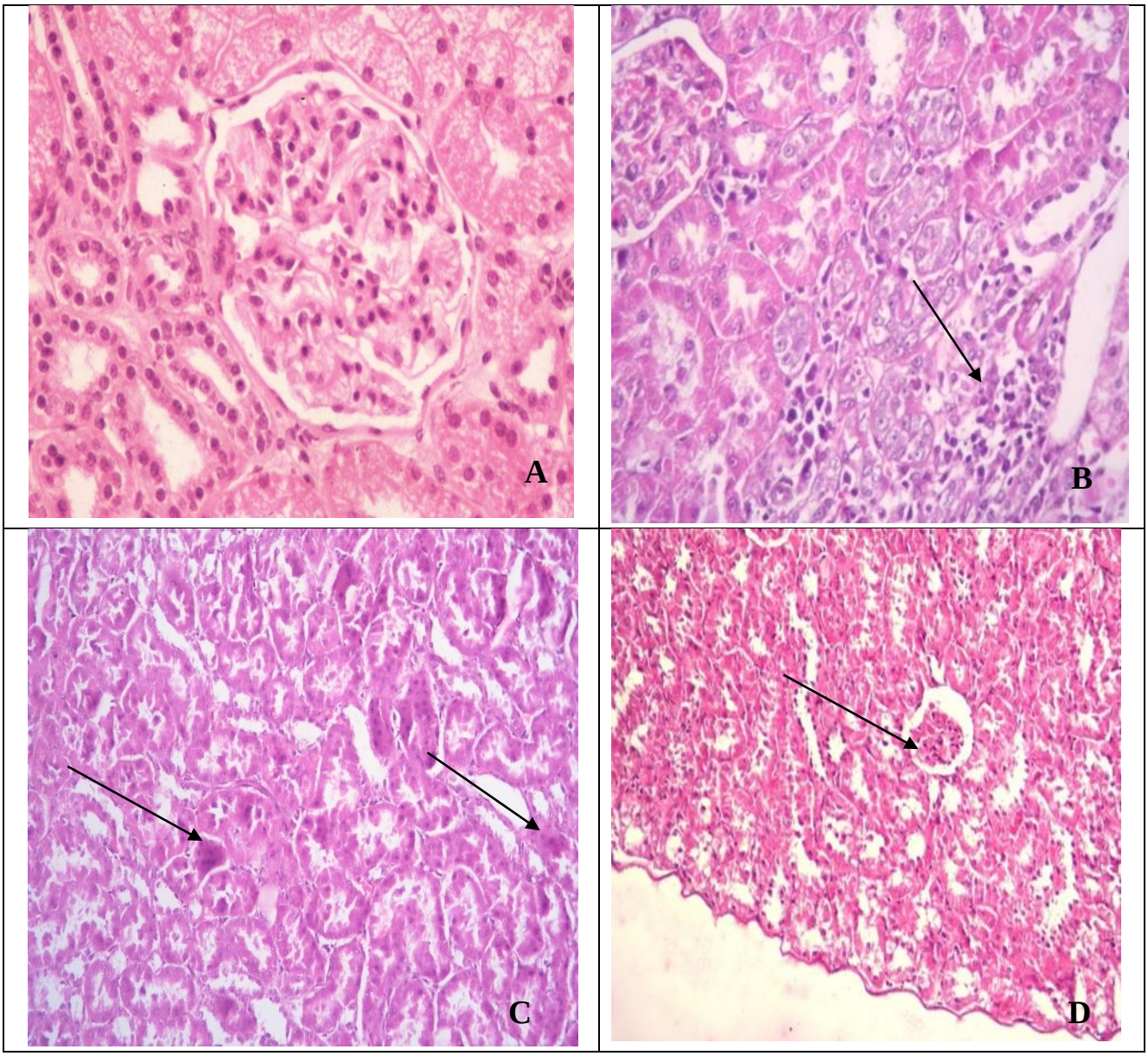

Figure (6): Effects of GA3 treatment on the kidney of rats after recovery period (R) for 2 weeks
Control recovery (G1R): showing normal kidney architecture.
(A) Kidney of group (G2R): some cells lining renal tubules were vesicular other cells showed necrosis (arrow).
(B) Kidney of group (G3R): necrosis of most of cells lining the renal tubules. Giant multinucleated cells were seen (arrows).
(C) Kidney of group (G4R): some cells lining the renal tubules were necrosed (arrow). & have mitotic division & were infiltrated with mononuclear inflammatory cells (carcinogenic stages).

V. DISCUSSION

Gibberellic acids (GA3) are a group of naturally occurring plant hormones that are utilized to promote leaf and stem elongation as well as cell division in plants. GA3 was utilized in many nations, including Egypt, to accelerate the growth of some vegetables and some fruits (such as tomatoes, cabbages, cauliflower, pepper, and olive). GA3 was identified by the WHO as a pesticide-related PGR. GA3 exposure can occur in industrial context or public

exposure by eating tainted food items. (Guleria et al. 2021).

In this study we found that GA3 altered activity and significant decrease in catalase enzyme activity. These findings came in agreement with Troudi et al. (2011) who found a decrease in superoxide dismutase, catalase, and glutathione peroxidase activities in plasma of both dams and their pups. Moreover, a significant decline was observed in plasma glutathione, nonprotein thiols, and vitamin C levels.

The results showed significant increase in the MDA level as an indicator for lipid peroxidation. The MDA level was reduced during the recovery period, but its values were still higher than the control rats due to the cumulative effect of GA3. Similarly, Sayed et al. (2022) demonstrated a significant rise in plasma levels of malondialdehyde, protein carbonyls, and advanced oxidation protein products in juvenile tilapia treated with GA3.

The hepatic lesions displayed vacuolation of the hepatic cells, clogged blood arteries, and necrosis of certain cells. Our results are consistent with alterations in liver enzymes that show cellular breakdown and loss of function and membrane integrity in the liver (Soliman et al. 2021). Additionally, Sakr et al. (2003) demonstrated that GA3 caused numerous histological alterations in the liver of rats, which our results corroborated. Heavy leucocytic infiltrations in the liver in animals treated with GA3 were one of the clinical signs seen. These leucocytic infiltrations were thought to be an immunological response of the organs to any potentially harmful substance. The findings are consistent with those made by Husseiny et al. 2020, who discovered that GA3 can have harmful effects on a variety of mesenchymal organs, including the liver.

The kidney lesions findings revealed vacuolation of the cells lining the renal tubules, congestion of blood vessels and periglomerular edema. Also, necrosis was noticed in certain cells. These lesions were coincided with the results found by Mona and Wafaa (2010) who demonstrated that numerous convoluted tubules in the renal cortex of the kidney had symptoms of degeneration in the form of vacuolation, desquamation, and even rupture after GA3 injection. The chronic GA3 group demonstrated substantial tubular dilatation with a large lumen, weak epithelium, desquamated cells in the lumen, and hyaline casts in the lumen of certain tubules, they further demonstrated. Any chronic kidney damage was associated with this picture of tubular shrinkage and interstitial inflammation. Our findings are consistent with those of Husseiny et al. (2020), who discovered that the main characteristics of GA3-treated groups included the development of an enlarged tubular lumen, an inflammatory response, the appearance of an atrophied Bowman's space, and tubular epithelial cell degeneration.

The current study supports earlier findings of Troudi et al. (2011) who discovered renal tissue injury in adult rats exposed to GA3 that was characterized by cytoplasmic vacuolization of the lining epithelial cells in the renal tubules, a degeneration of the glomeruli, and a congestion of blood vessels.

The lesions that appeared in the recovery period in different organs indicated that GA3 the liver is the organ of intoxication (Troudi et al. 2010). The kidney, on the other hand, is more vulnerable to chemical toxicity because to its high blood flow and its anatomically and functionally complex tubular cells, which also bioactivate some toxins. Our findings

in the recovery period came in agreement with Mona and Wafaa (2010) who discovered that cystic glomerular atrophy, acute tubular necrosis, degenerated podocytes, and thicker blood renal barrier had a cumulative effect that resulted in the development of cancer in the liver and kidney. The biochemical indicators of oxidative stress were linked to the histological alterations. Although these alterations were lessened in the recovery group, they did not return to normal, and the signs of oxidative stress were still evident. Similarly, Askar, & Ismaell (2012) reported that feeding chickens with GA3 led to numerous histological lesions in different organs including liver and that two-week withdrawal period did not ameliorate the effect of GA3. The lesions in the recovery period agreed with Troudi et al. (2010) found that giving GA3 to hens caused a variety of histological abnormalities in many organs, including the liver, and that a two-week withdrawal period had no influence on the effect of GA3. The recovery period lesions supported the findings of Troudi et al. (2010) who demonstrated that the 200-ppm dose used in their experiment caused an oxidative stress in both lactating mothers and their offspring without having a lethal effect. This finding supported the idea that GA3 can pass through milk. In fact, there was a buildup of GA3 in the mothers' and the pups' plasma, milk, stomachs, and kidneys.

VI. CONCLUSION & RECOMMENDATION

GA3 possess an oxidative stress damage to liver and kidney. The damage was directly proportional to the dose of GA3 intake and not recovered completely by time after stopping exposure to GA3. MDA in liver was increased by increase dose of GA3 intake. Catalase enzyme activity in liver was reduced by GA3 intake and activity was decreasing more in group received highest dose of GA3.pathologic changes in liver and kidney were directly proportional with dose of GA3 administered and this damage wasn't relieved by stopping exposure to GA3.

From all the foregoing findings that the improper use of PGRs may pose a risk to human health, particularly if they are amplified in the food chain. Use of GA3 and other comparable plant growth regulators should be cautious, and their levels in agricultural products should be regularly controlled.

VII. CONFLICT OF INTEREST

All authors declare that there are not any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work.

VIII. Funding:

The researchers were not financially assistance by any organization.

IX. REFERENCES

- Alsemeh, A.E., Moawad, R.S. & Abdelfattah, E.R. (2019): Histological and biochemical changes induced by Gibberellic acid in the livers of pregnant albino rats and their offspring: ameliorative effect of Nigella sativa. Anat Sci Int 94, 307–323(2019).
- Askar, A. A., & Ismaell, E. I. (2012): Effect of Gibberellic acid on some physiological; reproductive and hatchability parameters of laying hens during winter and summer seasons. Egyptian Journal of Animal Production, 49(1), 77-86.

- Fonger, G. C., Hakkinen, P., Jordan, S., & Publicker, S. (2014): The National Library of Medicine's (NLM) Hazardous Substances Data Bank (HSDB): background, recent enhancements and future plans. Toxicology, 325, 209-216.
- Guleria, S., Kumar, M., Khan, A., & Kaushik, R. (2021): plant hormones: physiological role and health effects. Journal of Microbiology, Biotechnology & Food Sciences, 11(1).
- Hussein, M. M., Ali, H. A., & Ahmed, M. M. (2015): Ameliorative effects of phycocyanin against Gibberellic acid induced hepatotoxicity. Pesticide Biochemistry and Physiology, 119, 28– 32. https://doi.org/10.1016/j.pestbp.2015.02.010
- Hussein, W. F., Farahat, F. Y., Abass, M. A., & Shehata, A. S. (2011): Hepatotoxic potential of Gibberellic Acid (GA3) in adult male albino rats. Life Sci J, 8(3), 373-383.
- Husseiny, N., Farag, A., Mohammed, H. (2020): 'Histological and Immuno-histochemical Study of Toxic Effect of Gibberellic acid Postnatally on Renal Cortex of Albino Rats', Egyptian Journal of Histology, 43(4), pp. 1070-1086.
- Iwan, P., Stepniak, J., & Karbownik-Lewinska, M. (2021): Cumulative Protective Effect of Melatonin and Indole-3-Propionic Acid against KIO3—Induced Lipid Peroxidation in Porcine Thyroid. Toxics, 9(5), 89.
- Khdar, Z. A., Le, T. M., Schelz, Z., Zupkó, I., & Szakonyi, Z. (2022): Stereoselective Synthesis and Application of GA3-Derived Aminodiols. International Journal of Molecular Sciences, 23(18), 10366.
- Khoubnasabjafari, M., Ansarin, K., & Jouyban, A. (2015): Reliability of malondialdehyde as a biomarker of oxidative stress in psychological disorders. BioImpacts: BI, 5(3), 123.
- Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. (2005): Nonalcoholic Steatohepatitis Clinical Research Network. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. HEPATOLOGY; 41:1313-1321.
- Material Safety Data Sheet. Gibberellic acid (2012): available at: https://www.finarchemicals.com/msds/Gibberellic%20acid.pdf last accessed at 13 january 2023
- Melo, R. C., Raas, M. W., Palazzi, C., Neves, V. H., Malta, K. K., & Silva, T. P. (2020): Whole slide imaging and its applications to histopathological studies of liver disorders. Frontiers in medicine, 6, 310.
- Milovanović, M., & Perišić, J. (2020): Advantages and limitations of using SPSS in teaching statistics. MEFkon 2020 innovation as an initiator of the development "innovations in the function of development", 274.
- Mona GA. and Wafaa FH. (2010): Influence of Gibberellic acid (GA3) on renal cortex of adult male albino rats (histological, immunohistochemical and biochemical Study). Egypt. J. Histol. Dec., 33(4): 767 – 780.
- Panda, D., Mohanty, S., Das, S., Sah, R. P., Kumar, A., Behera, L., & Tripathy, B. C. (2022): The role of phytochrome-mediated Gibberellic acid signaling in the modulation of seed germination under low light stress in rice (O. sativa L.). Physiology and Molecular Biology of Plants, 28(3), 585-605.
- Rahm, M., Atty, Y. A., Rahman, M. A., & Sabry, M. (2017). Structural changes induced by Gibberellic acid in the renal

cortex of adult male albino rats. MOJ Anat. Physiol, 3, 00080.

- Sakr S, Tosry A, Okdaha A and Sabah F. (2003): Gibberellin A3 Induced histological and histochemical Alterations in the Liver of Albino Rats. Science Asia., 29: 327-331.
- Sayed, A. E. D. H., Hamed, M., El-Sayed, A. A., Nunes, B., & Soliman, H. A. (2022): The mitigating effect of Spirulina (Arthrospira platensis) on the hemotoxicity of Gibberellic acid on juvenile tilapia (Oreochromis niloticus). Environmental Science and Pollution Research, 1-11.
- Soliman, H. A., Mantawy, M. M., & Hassan, H. M. (2010): Biochemical and molecular profiles of Gibberellic acid exposed albino rats. J Am Sci, 6(8), 224-229.6:18-23
- Soliman, M. M., Aldhahrani, A., Gaber, A., Alsanie, W. F., Shukry, M., Mohamed, W. A., & Metwally, M. M. (2021). Impacts of n acetyl cysteine on Gibberellic acid induced hepatorenal dysfunction through modulation of pro inflammatory cytokines, antifibrotic and antioxidant activity. Journal of Food Biochemistry, 45(4), e13706.
- Sonkar, S., Sharma, L., Singh, R. K., Pandey, B., Rathore, S. S., Singh, A. K., ... & Singh, S. P. (2021). Plant stress hormones nanobiotechnology. In Nanobiotechnology (pp. 349-373). Springer, Cham.
- Srivastava, A., Palsson, R., Kaze, A. D., Chen, M. E., Palacios, P., Sabbisetti, V., & Waikar, S. S. (2018): The prognostic value of histopathologic lesions in native kidney biopsy specimens: results from the Boston Kidney Biopsy Cohort Study. Journal of the American Society of Nephrology, 29(8), 2213-2224.
- Sun, X., Chen, F., Yuan, L., & Mi, G. (2020): The physiological mechanism underlying root elongation in response to nitrogen deficiency in crop plants. Planta, 251(4), 1-14.
- Tawfik S.M. (2015): Histological and immunohistochemical study on the effect of Gibberellic acid on the liver of adult male albino rats and the possible protective role of green tea. The Egyptian Journal of Histology 38(2): p 317-331, June 2015. | DOI: 10.1097/01.EHX.0000464778.90739.fc
- Troudi A., Mahjoubi Samet A. and Zeghal N. (2010): Hepatotoxicity induced by Gibberellic acid in adult rats and their progeny. Exp. and Toxicol. Pathol., 62 :637-642.
- Troudi, A., Amara, I. B., Soudani, N., Samet, A. M., & Zeghal, N. (2011): Oxidative stress induced by Gibberellic acid on kidney tissue of female rats and their progeny: biochemical and histopathological studies. Journal of physiology and biochemistry, 67(3), 307-316.

التأثيرات السامة شبه المزمنة لحمض الجبريليك على الكبد والكلى في الجرذان البيضاء البالغة: دور الإجهاد التأكسدي

الملخص العربي

مقدمة: تستخدم العديد من المواد الكيميائية حاليًا في الزراعة ومن بينها منظمات نمو النبات على نطاق واسع. يلعب حمض الجبريليك (GA3) أدوارًا مهمة في العديد من العمليات الخلوية بما في ذلك تعزيز استطالة الساق، وتعبئة احتياطيات الغذاء في إنبات بذور الحشائش، والأحداث، والتعبير الجنسي.

الهدف من البحث: الكشف عن التأثيرات السمية المحتملة لحمض الجبريليك على أنسجة الكبد والكلى

المنهجية: تم إجراء البحث على عدد 75 من فئران ألبينو البالغة. قسمت الجرذان إلى مجموعتين. المجموعة الأولى وهي المجموعة العلاجية والتي تم إعطاء جرعات مختلفة عدا المجموعة الفرعية الاولي والثانية والتين اعتبرتا المجموعة الضابطة والمجموعة الضابطة الموجبة. تم إعطاء المجموعة العلاجية الضابطة الموجبة هيدروكسيد صوديوم مخفف في ماء مقطر وهو المذيب المستخدم لإذابة حمض الجبريليك. تم إعطاء المجموعة العلاجية الأولي 10/1 من الجرعة النصفية المميتة لحمض الجبريليك. تم إعطاء المجموعة العلاجية الثانية 20/1 من الجرعة النصفية المميتة من حمض الجبريليك. تم إعطاء المجموعة العلاجية الثالثة 40/1 من الجرعة النصفية المميتة لحمض الجبريليك. استمر إعطاء حمض الجبريليك لمدة 12 أسبوع وتم ذبح الجرذان وعمل تحليل لعوامل الأكسدة (مستوي مالون ثنائي الألدهيد ونشاط إنزيم الكتاليز في الكبد) وحمض فحص خلوي للكبد والكلي.

باقي الجرذان (25 جرذ) تم تقسيمهم على 5 مجموعات فرعية وتم إعطاء نفس الجرعات كالمجموعات السابقة لمده 12 أسبوع، ولكن لم يتم ذبحهم إلا بعد مرور أسبوعين اخرين لبيان مدي التأثير التراكمي لحمض الجبريليك في الجسم.

النتائج: كشف قياس دلالات الأكسدة على ارتفاع ملحوظ لمادة مالون ثنائي الألدهيد ونقص بنشاط إنزيم كتاليز في الكبد. كما أن الفحص النسيجي المرضي للكبد والكلي كشف عن وجود نخر ملحوظ في الأنسجة ولم تستطع فترة الشفاء استعادة هذه التغيرات المرضية بسبب الآثار التراكمية لحمض الجبريليك على الكبد والكلى.

الاستنتاجات: التعرض لحمض الجبريليك يؤدي إلى تأثير ضار ملحوظ بسبب زيادة الحمل المؤكسد

التوصيات: حمض الجبريليك له أخطار على صحة الإنسان بسبب الأضرار التأكسدية للأنسجة مثل الكبد والكلى. يجب أن يكون استخدام حمض الجبريليك حذرًا، ويجب التحكم في مستواه في المنتجات الزراعية بانتظام