DJS Vol. 46(1) (2023) –pp.10-22 ISSN: 1012-5965

Delta Journal of Science

Available online at **https://djs.journals.ekb.eg/**

Research Article

ZOOLOGY

Mechanistic study on the metformin treatment effect on the oxidative stress caused by doxorubicin in albino rat liver

Fayza. M. Shouman[1], Karim S. El-Said[2], Mona M. Hegazi[1], Mona M. Elwan[1], Ezar. H. Hafez[1]

[1] Zoology Department, Faculty of Science, Tanta University

[2] Biochemistry Division, Chemistry Department, Faculty of Science, Tanta University

Corresponding author: Fayza. M. Shouman ***e-mail:*** fayzashouman195@yahoo.com

Received; 18/12/2022 Accepted: 23/1/2023

KEY WORDS

Doxorubicin;

Metformin;

oxidative stress;

Antioxidants;

Hepatotoxicity;

ABSTRACT

Oxidative stress was induced in male albino rat by doxorubicin (DOX) treatment. This study aims to evaluate the metformin (Met) impact on the DOX induced-oxidative stress in rats. Forty male albino Wistar rats grouped under four categories; Group I served as the control group while Group II received four doses of DOX (4 mg/kg) i.p, twice a week. Group III was treated with Met (250 mg/kg/day) by gavage for 14 days. Group IV was treated with DOX as in group II and with Met as in group III. All rats were killed when the experiment was over. Collection of liver tissues was done for biochemical, molecular, and histopathological investigations. According to the findings, DOX treatment significantly reduced CAT and SOD activity, however, treating DOX-injected rats with Met significantly reduced the CAT and SOD activity in the liver. GPx activity was significantly increased in the DOX-intoxicated rats, treatment of DOX-injected group with Met led to significant decrease in the GPx activity. Treatment of DOX-injected group with Met led to decrease in GST activity. DOX-injected rats that treated with Met showed a substantial increase in the levels of gene expression of CAT and SOD, however, GPx and GST gene expression were down- regulated. Met improved histologically the liver tissue of albino rat received DOX. These findings revealed the Met enhanced effect on antioxidant enzyme gene expression and the simple effect on enzyme activity.

Introduction

Doxorubicin (DOX) is a chemotherapy drug used to treat different cancer types however, the use of anthracycline drugs is limited due to their side effect which actuates hepatotoxicity as well as cardiotoxicity **(Injac *et al*., 2009; Thorn *et al*., 2011)**. Doxorubicin suppresses the topoisomerase II enzyme by intercalating witshin DNA base pairs, which results in DNA damage and the initiation of apoptosis **(Doroshow, 2019)**. The antitumor effect mechanism of DOX returns to alterations in DNA and the formation of free radicals which play a crucial role in DOX toxicity **(Injac *et al*., 2008)**. The pathway indicates the production of semiquinone-type free radical molecules by the NADPH-dependent reductase enzyme. It has been established that hydroxyl radical induces DNA damage, lipid peroxidation, and protein inactivation **(Sinha, 2020)**.

Reactive oxygen species (ROS) is a normal byproduct of oxygen metabolism. The normal cell contains low levels of ROS, which is essential for cell functions **(Herb *et al*., 2021).** At the same time, the high expression of ROS or inefficient getting rid of ROS can oxidize some cell component, damage DNA, make the cell deviate from its true function pathway, and lead to cell mutation and cancer. Reactive Oxygen Species can be generated by external factors such as radiation, drugs, heavy metals, or by internal biochemical processes **(Muthukumar & Nachiappan, 2010).** In the case of radiation exposure, the water molecule loses an electron and is converted to hydrogen peroxide, hydroxyl radical, superoxide radical, and oxygen. The antioxidant system maintains this balance by keeping ROS at low levels.

The antioxidant system inhibits the oxidation reaction, which produces some types of free radicals that damage the cell. The antioxidant system stops the reactive oxygen species formation and maintains them at an optimum state **(Rhee, 2006).** There are two types of antioxidants: hydrophilic antioxidants which protect the blood plasma and cytosol from the oxidants, and lipophilic antioxidants which prevent lipid peroxidation and protect the cell membrane (**Ali *et al*., 2020).** Antioxidants may be naturally formed in the body or supplemented by the diet such as vitamins **(Vertuani *et al*., 2005).**

Metformin (Met) is known by its trade name glucophage which reduces glucose absorption and targets beta-cell

sensitivity therefore, it is used to treat type 2 diabetes **(Bennett *et al.*, 2011; Inzucchi *et al.*, 2012)**. The previous study investigates that Met inhibits the mitochondrial complex 1 by suppressing the electron transfer from NADHH. It is well known that NADH participates ultimately in oxidative stress and ROS production so, the blockage of this compound leads to decreased ROS production and enhance antioxidant response **(Fujii *et al.*, 2022)**. This study aims to investigate impact of Met treatment on the molecular, biochemical, and histopathological alterations induced by DOX in rats.

Materials and methods

Chemicals

Doxorubicin (DOX) and metformin (Met) were purchased from local pharmacy, Tanta city, Egypt. All biochemical kits were purchased from Bio-diagnostic Company, Egypt.

Animals and experimental design

Forty albino males prior to the experiment, Wistar rats (130–220g) were adapted for a week by receiving a regular meal and water. Four groups of rats were formed, with group I serving as the control group and group II receiving four doses of DOX. (4 mg/kg i.p; twice a week); group III: was treated with Met (250 mg/kg/day) by gavage for 14 days; group IV: was treated with DOX as in group II and with Met as in group III. All rats were weighted, anesthetized and sacrificed at the end of the experiment. The percentages of body weight changes were calculated. For biochemical and histological examinations, liver tissues were gathered.

Biochemical and gene expression analysis

Parts from liver tissues of each group were collected and stored at -80 $^{\circ}$C for determination of the oxidants/antioxidant's biomarkers and gene expression analysis by RT-PCR. Homogenize each gramme of liver tissue in a cold buffer containing 50 mM potassium phosphate (pH 7.4), 1 mM EDTA, and 1 mL/L Triton X-100. Activities of catalase (CAT) and superoxide dismutase (SOD) were assessed following the methodology of **Aebi, (1984); Paoletti and Mocali, (1990)**, respectively. Glutathione peroxidase (GPx) was assessed according to the methods of **Paglia and Valentine, (1967)** assay. The technique developed by **Habig *et al.*, (1974)** was used to test the Glutathione-S-Transferase (GST) activity.

For molecular analysis, real-time PCR was used to assess CAT, SOD, GPx, and GST genes expression in the liver tissues following the manufacturer protocol (Thermo Scientific, Waltham, MA, USA, # K0221). Using the β-actin as housekeeping gene.

Histopathological studies

The liver samples were preserved in 10% neutral formalin, dried in 70% ethyl alcohol, cleaned in xylene, and then embedded in paraffin for blocking. By using a microtome, the extremely thin sections are sliced off in a ribbon form. This ribbon is moved to a warm water bath which allowed it to float then it can be picked up on a charged slide which reduces washing the section off the slide and increases the adhesion of the tissue to the slide. The tissues were subject to a specific staining technique. As the cells are colorless and transparent, hematoxylin and eosin stains are used which enables the tissue structure to be visible and contrast. In order to protect the tissue during the microscopic examination, a cover is installed on the specimen on the slide.

Statistical analysis

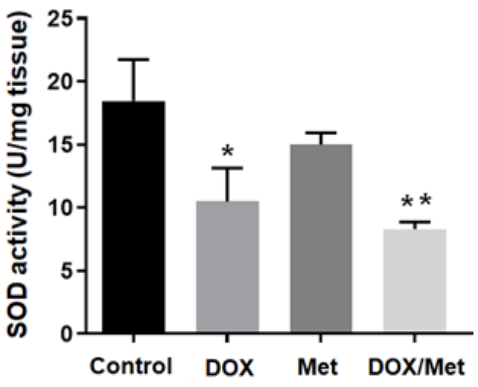
In this study, the Graph Pad Prism 9 software was used for the statistical analyses. For statistical evaluation, the mean difference of both enzyme activity and gene expression was assessed by one-way ANOVA to check the DOX and Met effect followed by multiple comparisons Dunnett's test (compare all vs. controls). P values ≤ 0.05 were considered statistically significant.

Results

Effect of DOX or/and Met treatment on the antioxidant enzymes of rats

The outcomes demonstrated that, in the DOX-injected group of rats, CAT and SOD activities were considerably lower ($P \leq 0.05$) than in the control group. The hepatic CAT and SOD activity considerably reduce after 14 days of Met treatment in DOX-injected rats **(Fig. 1)**. Furthermore, GPx activity was significantly increased in the DOX-intoxicated rats to 17.94 ± 2.05 U/g tissue, in contrast to the control group, however, treatment of DOX-injected group with Met caused significant decrease in the GPx activity when compared to the DOX-injected rats alone **(Fig. 2)**. As compared to the control group, the DOX-injected group showed significant decrease ($P \leq 0.05$) in the GST activities. Treatment of DOX-injected group with Met led to decrease in GST activity to 14.47 ± 0.83 U/g tissue when compared to the DOX-injected group that represented 19.1 ± 4.37 U/g tissue for GST activity **(Fig. 2)**.

(A)



(B)

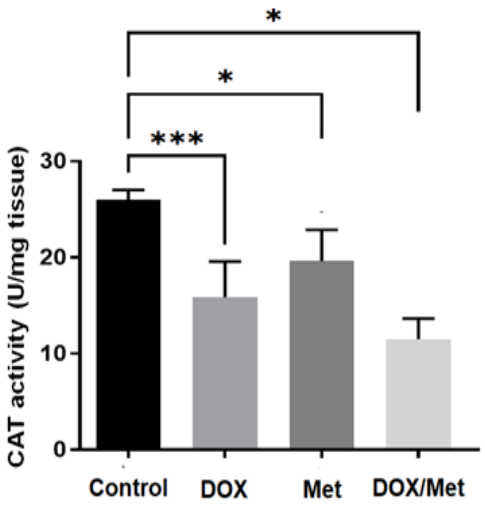


Fig. (1): Activities of hepatic superoxide dismutase (SOD) (A) and catalase (CAT) (B) in the various study groups. All data were reported as means with standard deviations, and *P 0.05 indicated statistical significance.

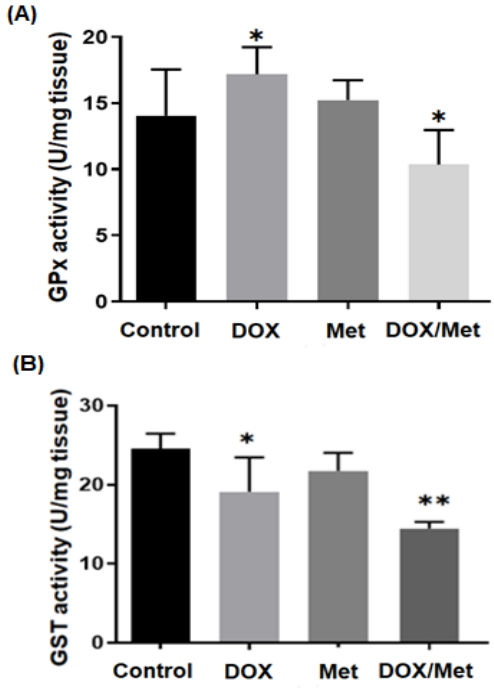


Fig. (2): Glutathione-peroxidase (GPx) (A), and Glutathione-S-transferase (GST) (B) activities in the livers of the various study groups. All data were reported as means with standard deviations, and *P 0.05 indicated statistical significance.

Molecular analysis of the antioxidant enzymes genes by RT-PCR

The injection of rats with DOX (4 mg/kg) i.p. twice a week for 14 days led to significant decrease in the gene expression of hepatic CAT when compared with normal control group. A significant up-regulation in the mRNA expression level of the CAT gene was reported in the hepatic tissues of DOX-injected group that treated with Met when compared with rats that injected with DOX alone **(Fig. 3A)**. The data revealed that there were no significant changes in SOD gene expression were observed between the negative control and DOX-injected groups. The results of qPCR showed an increase in the relative mRNA expression level of the SOD gene in the liver tissues of DOX-injected group that treated with Met, which represented 1.41±0.53-fold using β-actin housekeeping gene when compared with control groups **(Fig. 3B)**.

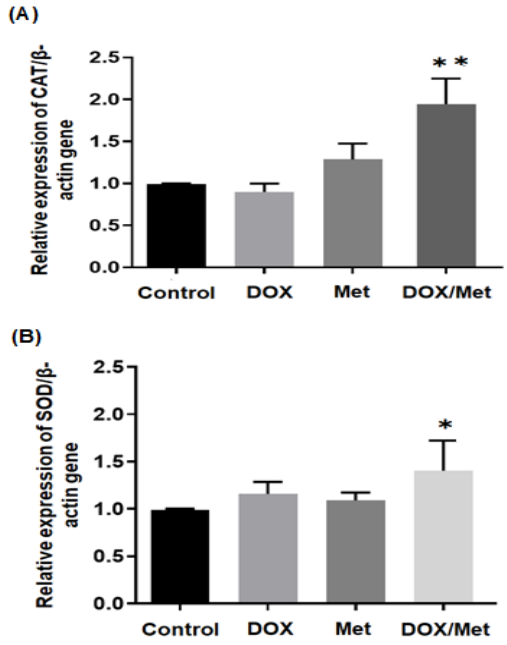


Fig. (3): Gene expression analysis of CAT **(A)**, and SOD **(B)** genes by RT-PCR in the different groups under the study, shows the relative expression of using *β*-actin housekeeping gene. The values represented as means ± S.D. $^{*}P \leq 0.05$ was considered to be statistically significant.

The mRNA relative expression level of GPx enzyme was detected in the liver tissues of all groups under the study. The results of qPCR analysis showed that there was significant increase in the fold of change of GPx expression level up to 1.62±0.16 using *β*-actin housekeeping gene when compared with their control groups that represented 1.00 ± 0.07. Treatment of DOX-injected rats with Met restored the hepatic mRNA relative expression of the GPx gene close to the normal control groups (1.19±0.09), when compared to the group of rats that injected with DOX alone **(Fig. 4A)**. Furthermore, the results showed that injection of rats with DOX resulted in significant increase in the mRNA relative expression level of GST genes by almost 2-folds when compared with normal control groups that almost represented 1.00. However, the data of RT-PCR analysis showed that treating DOX-injected rats with Met resulted in a significant decrease in the hepatic mRNA expression level of the GST genes up to 1.29 ± 1.30 when compared with rats that injected with DOX alone **(Fig. 4B)**.

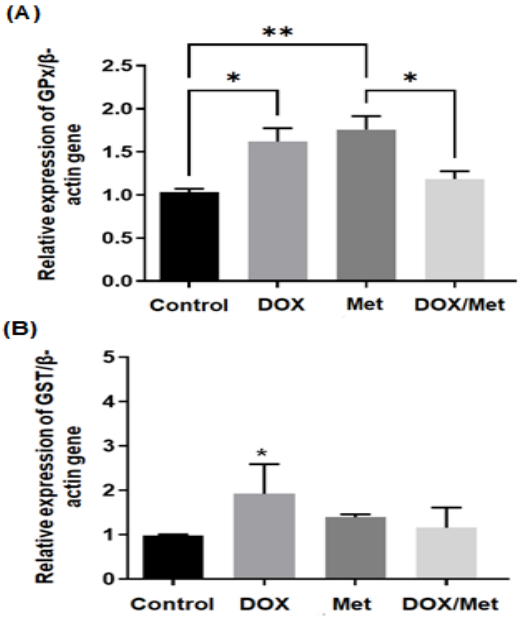


Fig. (4): Gene expression analysis of GPx (A), and GST (B) genes by RT-PCR in the different groups under the study, shows the relative expression of using *β*-actin housekeeping gene. The values represented as means ± S.D. $^{*}P \leq 0.05$ was considered to be statistically significant.

Histopathological investigations of the liver tissues in the different groups under the study

Hepatocyte architecture and hepatic lobulation were seen in normal condition in liver tissue samples from control rats. Narrow blood sinusoids surrounded by an endothelial cell layer and Kupffer cells alternating with hepatic strands. Hepatocytes revealed centrally located nuclei and normal distributed chromatin **(Fig. 5A)**. Rats given DOX injections had substantially altered hepatic architecture visible in their liver sections, severe congested and dilated central vein; mostly hepatocytes were degenerated with vacuolated cytoplasm, others with some nuclear changes such as uneven blood sinusoids with prominent Kupffer cells and pyknotic nuclei were observed **(Fig. 5B)**. Rats given Met in the liver showed conventional hepatic architecture and healthy radiating hepatocyte, few numbers are degenerated, regular central veins, and slight mononuclear infiltration and Blood sinusoids containing phagocytic Kupffer cells that were activated were noticed **(Fig. 5C)**. Rat liver section following treatment with (DOX/Met) showing improvement in the hepatic structure that represented by normal and regular central vein, normal radiating hepatic strands with normal central nuclei, few numbers of hepatocytes are binucleated, slightly widening blood sinusoids with normal Kupffer cells **(Fig. 5D)**.

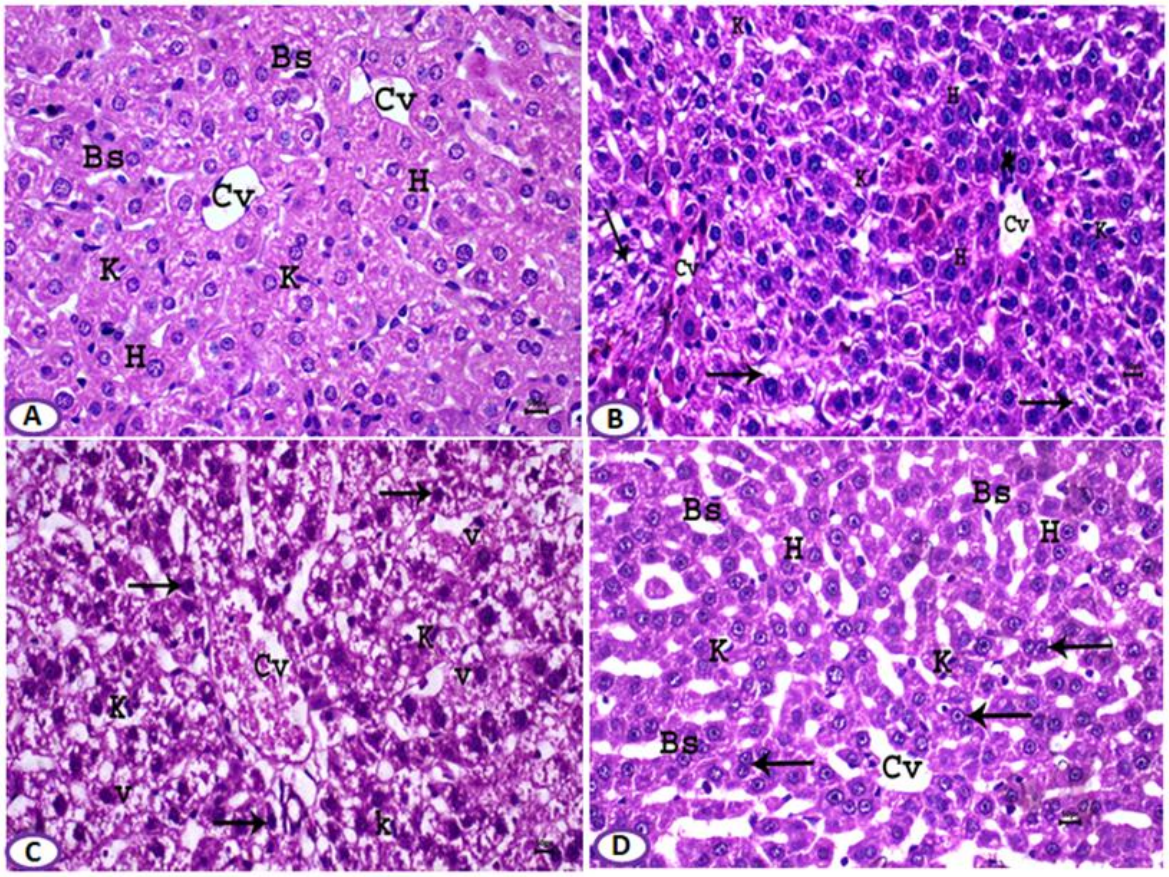


Fig. (5): (A) The liver of the healthy control group displays regular central veins (cv) and a normal-appearing hepatic anatomy, mostly hepatocytes are normal (H), with Kupffer cells (K) and normal blood sinusoids (Bs). (B) Liver section of rats administered with Met showing normal like structure of hepatic structure; regular central veins (Cvs), slight mononuclear infiltration (*) contains Kupffer cells that are active (K) (C) Liver section of rats injected with DOX exhibits marked disorganization of hepatic architecture, severe congested and dilated central vein (Cv), The majority of the deteriorated hepatocytes had vacuolated cytoplasm (V), others with pyknotic nuclei (arrows), Uneven blood sinusoids with discrete Kupffer cells (K) (D) Rat liver section following treatment with DOX/Met showing improvement in the hepatic organization that represented by normal and regular central vein (Cv), A few normal binucleated hepatocytes (arrows) and slightly broadening blood sinusoids (Bs) with normal Kupffer cells may be seen in the normal radiating hepatocytes (H) with normal nuclei (X 400).

Discussion

Despite the widespread use of DOX as an antitumor for many solid cancers, the toxicity it causes to many organs, particularly the liver has led to a draw back in its use as chemotherapy. DOX-induced hepatotoxicity is a consequence of oxidative stress associated with the overproduction of reactive oxygen species. Regulation of ROS generation and redox balance is an approach to reduce doxo-induced toxicity.

The present data shows a considerable increase in MDA levels in hepatic tissue

when albino rats were exposed to four 4mg/kg) twice a week. **Henninger *et al*., (2012)** found that the acute doses of DOX induced the oxidative stress and hepatotoxicity **(Henninger *et al*., 2012).** The exposure to DOX had a direct damaging effect on the antioxidant enzymes of albino rat liver. In the present study the CAT, GPX, SOD, GST, and GR activity in the liver of albino rat exposed to DOX showed a significant decline. In this experiment, the amount of oxidative stress caused by DOX treatment was so great that the antioxidant enzymes lost their potential to increase their activity as a normal response. Also, Dox's group of 10 rats, one of whom died on the 14th day, and the rest of rats worsened, and they were on the verge of death as a result of hepatotoxicity and cardiotoxicity. On the other side, the gene expression level of CAT and GR in the liver of albino rat exposed to DOX was decreased, while superoxide dismutase slightly increased, and GPX and GST increased significantly. Hence, this data confirms that DOX increased oxidative stress and decreased the activity and gene expression of some enzymes.

DOX stimulates the inflammatory response by releasing ROS which promote apoptosis by activating caspase-3, regulating P53 tumor suppressor signal, and releasing cytochrome c doses of DOX (**Mukherjee *et al*., 2003).** All previous studies focused on Silent information regulator 1 (Sirt1) protecting role against Dox-induced cardiotoxicity but, there is no study confirming its role against hepatotoxicity. The previous studies revealed the Sirt1 role in P53 signal regulation, NF-κB suppression, myocarditis regulation and apoptosis **(Han *et al*., 2008; Zhao *et al*., 2015).** Sirt1 overexpression protect heart through increasing the cell survival and resistance and up-regulating the antioxidants actions **(Brookins Danz *et al*., 2009).** The present data shows histologically damaging in hepatocytes represented in thrombosis and congestion in central vein, degeneration in hepatocytes, widely dilatation in blood sinusoid of Kupffer cell, and nuclear pyknosis.

As the Met primary effect is the mitochondrial complex I inhibition, the drug exerts its effect by reducing ROS generation at the complex 1, Preventing cell death caused by oxidative stress, and stopping mitochondrial-mediated apoptosis. The mitochondrial complex I inhibition mechanism is done by direct interaction with NADH dehydrogenase 3 core subunit and on mGP_{DH} (mitochondrial glycerophosphate dehydrogenase) which decrease the NADH oxidation, reduce the

consumption of oxygen, and reduce the pumping of proton through the inner membrane of mitochondria **(Vial *et al.*, 2019).**

In this research, the albino rat which received only daily doses of Met for two weeks show a normal TBARS levels in liver tissue. Also, there was no considerable change in the antioxidant enzymes (CAT, GPX, SOD, GST, and GR) activity, it was almost like the control. The gene expression level of glutathione reductase in the liver of albino rat injected with daily doses of Met for two weeks was still decline, while SOD and GST were just too high, and CAT and GPX were very high. This confirms that Met doses alone did not influence oxidative stress or the activity of antioxidant enzymes either up or down. Also, its effect on the gene expression of some enzymes was slight,

So the results of this group were closer to the control. The previous studies emphasized the anti-oxidative role of Met and its hepato-protective role which markedly attenuate the oxidative stress by reducing malondialdehyde and protein carbonyl content **(Lee *et al.*, 2020).**

The results in this experiment indicated that the exposure to both doses of DOX and daily doses of Met led to a significant increase in the level of MDA and a sharp decline in the activity level of all antioxidant enzymes. The results showed a sharp decrease in the level of the gene expression of GR enzyme, a marked increase in the level of GST and GPX enzyme, and a significant increase in the level of SOD and CAT enzyme. The data from previous studies from liver cells recommended that respiratory-chain complex 1 inhibition by Met may need a long time, and a very slow penetration into the mitochondria **(Apostolova *et al.*, 2020).** The histopathological alterations noticed in liver of the untreated DOX injected group were represented by marked disorganization of the hepatic structure, severe congestion of blood vessels and mostly hepatocytes were degenerated with vacuolated cytoplasm, others with some nuclear changes such as irregular blood sinusoids and pyknotic nuclei with distinct and active Kupffer cells were observed. The liver damage may result from the oxidative stress brought on by the reactive intermediates of doxorubicin, specifically semiquinone, which is formed from DOX by radical intermediates production. These radical intermediates interact with cellular macromolecules to produce ROS, which then causes cytological damage **(Shivakumar *et al.*, 2012).** Liver sections of Met groups exhibited normal like appearance of the hepatic architecture and liver sections of

(DOX/Met) treated group showed noticed improvement in the hepatic construction represented by normal radiating hepatocytes and normal blood vessels with slight histopathological changes. These results were agreement with (Sadeghi et al., 2019) who stated that Met reduced oxidative stress by arresting reactive nitrogen species such as NO at an intracellular level and prevented hepatic damage via the suppression of specific enzymes that are responsible for protein oxidation and lipid peroxidation.

In conclusion, treatment of DOX-injected rats with Met led to significant decrease in the activity of CAT, SOD, and GST, enzymes in hepatic tissue. However, this treatment resulted in up-regulation in the gene expression levels of CAT and SOD.

References

Ali, S. S., Ahsan, H., Zia, M. K., Siddiqui, T., & Khan, F. H. (2020). Understanding oxidants and antioxidants: Classical team with new players. *J. Food Biochem.,* 44(3)e 13145.

Apostolova, N., Iannantuoni, F., Gruevska, A., Muntane, J., Rocha, M., & Victor, V. M. (2020). Mechanisms of action of metformin in type 2 diabetes: Effects on mitochondria and leukocyte-endothelium interactions. *Redox Biol.,* 34:101517.

Bennett, W. L., Maruthur, N. M., Singh, S., Segal, J. B., Wilson, L. M., Chatterjee, R., Marinopoulos, S. S., Puhan, M. A., Ranasinghe, P., Block, L., Nicholson, W. K., Hutfless, S., Bass, E. B., & Bolen, S. (2011). Comparative effectiveness and safety of medications for type 2 diabetes: An update including new drugs and 2-drug combinations. *Ann. Intern.*, 154(9): 602-613.

Brookins Danz, E. D., Skramsted, J., Henry, N., Bennett, J. A., & Keller, R. S. (2009). Resveratrol prevents doxorubicin cardiotoxicity through mitochondrial stabilization and the Sirt1 pathway. *Free Radic. Biol. Med*., 46(12): 1589- 1597.

Doroshow, J. H. (2019). Mechanisms of Anthracycline-Enhanced Reactive Oxygen Metabolism in Tumor Cells. *Oxid. Med. Cell. Longev, 2019-p.14*

Fujii, J., Homma, T., & Osaki, T. (2022). Superoxide Radicals in the Execution of Cell Death. *J. Antioxid*. 11(3): 501.

Han, M. K., Song, E. K., Guo, Y., Ou, X., Mantel, C., & Broxmeyer, H. E. (2008). SIRT1 Regulates Apoptosis and Nanog Expression in Mouse Embryonic Stem Cells by Controlling p53 Subcellular Localization. *Cell Stem Cell, 2*(3): 241-251.

Henninger, C., Huelsenbeck, J., Huelsenbeck, S., Grösch, S., Schad, A., Lackner, K. J., Kaina, B., & Fritz, G. (2012). The lipid lowering drug lovastatin protects against doxorubicin-induced hepatotoxicity. *Toxicol*,, 261(1): 66-73.

Herb, M., Gluschko, A., & Schramm, M. (2021). Reactive Oxygen Species: Not Omnipresent but Important in Many Locations. *Front. Cell Dev. Biol*, 9: 2503. https://doi.org/10.3389/fcell.2021.716406

Injac, R., Perse, M., Obermajer, N., Djordjevic-Milic, V., Prijatelj, M., Djordjevic, A., Cerar, A., & Strukelj, B. (2008). Potential hepatoprotective effects of fullerenol C60(OH)24 in doxorubicin-induced

hepatotoxicity in rats with mammary carcinomas. *J. Biomat.* 29: 3451-3460.

Injac, R., Radic, N., Govedarica, B., Djordjevic, A., & Strukelj, B. (2009). Protective effects of fullerenol against chronic doxorubicin-induced cardiotoxicity and hepatotoxicity in rats with colorectal cancer. *Hem. Ind.*, 63: 259- 268.

Inzucchi, S. E., Bergenstal, R. M., Buse, J. B., Diamant, M., Ferrannini, E., Nauck, M., Peters, A. L., Tsapas, A., Wender, R., & atthews, D. R. (2012). Management of hyperglycemia in type 2 diabetes: A patient-centered approach. *Diabetes Care*, 35(6): 1364- 1379.

Lee, C. H., Han, J. H., Kim, S., Lee, H., Kim, S., Nam, D. H., Cho, D. H., & Woo, C. H. (2020). Metformin ameliorates bile duct ligation-induced acute hepatic injury via regulation of ER stress. *BMB Rep.*, 53(6):311- 316

Mukherjee, S., Kumar Banerjee, S., Maulik, M., Kumar Dinda, A., Talwar, K. K., & Kumar Maulik, S. (2003). Protection against acute adriamycin-induced cardiotoxicity by garlic: Role of endogenous antioxidants and inhibition of TNF-α expression. *BMC Pharmacol*, 3: 1-9.

Muthukumar, K., & Nachiappan, V. (2010). Cadmium-induced oxidative stress in Saccharomyces cerevisiae. *Indian J Biochem Biophys*, 47(6): 383-387.

Rhee, S. G. (2006). H2O2, a necessary evil for cell signaling. In *Science*. 312(5782): 1882- 1883.

Sadeghi, H., Jahanbazi, F., Sadeghi, H., Omidifar, N., Alipoor, B., Kokhdan, E. P., Mousavipoor, S. M., Mousavi-Fard, S. H., & Doustimotlagh, A. H. (2019). Metformin attenuates oxidative stress and liver damage after bile duct ligation in rats. *Res Pharm Sci*, *14*(2)

Sinha, B. K. (2020). Role of Oxygen and Nitrogen Radicals in the Mechanism of Anticancer Drug toxicity. *J Cancer Sci Ther*, 12(1): 10-18.

Thorn, C. F., Oshiro, C., Marsh, S., Hernandez-Boussard, T., McLeod, H., Klein, T. E., & Altman, R. B. (2011). Doxorubicin pathways: Pharmacodynamics and adverse effects. *PHARMACOGENET GENOM*, 21(7): 440–446.

Vertuani, S., Angusti, A., & Manfredini, S. (2005). The Antioxidants and Pro-Antioxidants Network: An Overview. *Curr*, 10(14): 1677-1694

Vial, G., Detaille, D., & Guigas, B. (2019). Role of mitochondria in the mechanism(s) of action of metformin. *Front Endocrinol* .,10: 294 p.8.

Zhao, L., An, R., Yang, Y., Yang, X., Liu, H., Yue, L., Li, X., Lin, Y., Reiter, R. J., & Qu, Y. (2015). Melatonin alleviates brain injury in mice subjected to cecal ligation and puncture via attenuating inflammation, apoptosis, and oxidative stress: the role of SIRT1 signaling. *J. Pineal Res*, *59*(2):230-239.

دراسة آلية عن تأثير علاج الميتفورمين على الإجهاد التأكسدي الناجم عن دوكسوروبيسين في كبد الجرذان البيضاء

ا/ فايزة شومان[١]، ا.د/ ايذار حافظ[١] ،ا.د/ مني حجازي[١]، ا.د/ كريم سامي[٢]، ا.د/ مني علوان[١]

[١] قسم علم الحيوان ـ كلية العلوم- جامعة طنطا

[٢] شعبة الكيمياء الحيوية- قسم الكيمياء ـ كلية العلوم- جامعة طنطا

تم إحداث الإجهاد التأكسدي في ذكور الجرذان البيضاء عن طريق علاج دوكسوروبيسين (DOX). تهدف هذه الدراسة إلى تقييم تأثير الميتفورمين (Met) على الإجهاد التأكسدي الناجم عن DOX في الفئران. أربعون ذكور جرذان بيضاء مجمعة تحت أربع فئات ؛ خدمت المجموعة الأولى كمجموعة تحكم بينما تلقت المجموعة الثانية أربع جرعات من DOX (4 مجم / كجم) آي بي مرتين في الأسبوع. عولجت المجموعة الثالثة بـ Met (250 مجم / كجم / يوم) بالتزقيم لمدة 14 يوم. عولجت المجموعة الرابعة بـ DOX كما في المجموعة الثانية ومع التقابل كما في المجموعة الثالثة. قُتلت جميع الفئران عندما انتهت التجربة. تم جمع أنسجة الكبد لإجراء الفحوصات البيوكيميائية والجزيئية والنسيجية. وفقًا للنتائج ، قلل علاج DOX بشكل كبير من نشاط CAT و SOD ، ومع ذلك ، فإن علاج الفئران المحقونة بـ DOX مع Met يقلل بشكل كبير من نشاط CAT و SOD في الكبد. تم زيادة نشاط GPx بشكل كبير في الفئران المصابة بـ DOX ، وأدى علاج المجموعة المحقونة بـ DOX مع Met إلى انخفاض كبير في نشاط GPx. أدى علاج المجموعة المحقونة بـ DOX مع Met إلى انخفاض نشاط GST. أظهرت الفئران المحقونة بـ DOX والتي عولجت بـ Met زيادة كبيرة في مستويات التعبير الجيني لـ CAT و SOD ، ومع ذلك ، تم تقليل التعبير الجيني GPx و GST. التقى تحسن نسيجيا أنسجة الكبد من الجرذان البيضاء تلقى DOX. كشفت هذه النتائج عن تأثير Met المعزز على التعبير الجيني للإنزيم المضاد للأكسدة والتأثير البسيط على نشاط الإنزيم.