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Pioglitazone ameliorates doxorubicin-induced hypothyroidism and cardiotoxicity in rat models

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Abstract. – OBJECTIVE: The anticancer drug doxorubicin (DOX) is effective but is associated with complications such as hypothyroidism and cardiotoxicity. Pioglitazone (PIO), which is used to treat diabetes mellitus, has shown potential for treating hypothyroidism and cardiac dysfunction. Therefore, this study explores whether PIO can also ameliorate DOX-induced hypothyroidism and cardiotoxicity.

MATERIALS AND METHODS: Forty female Wistar rats were separated into control and three treated groups (DOX, PIO, and DOX+PIO), and their blood samples were examined for the thyroid hormones, including thyroid-stimulating hormone (TSH), thyroxine in total and free forms (T4 and FT4, respectively), and triiodothyronine in total and free forms (T3 and FT3, respectively), and the cardiotoxicity biomarkers [troponin I, creatine kinase (CK), and creatine kinase-myocardial band (CK-MB)].

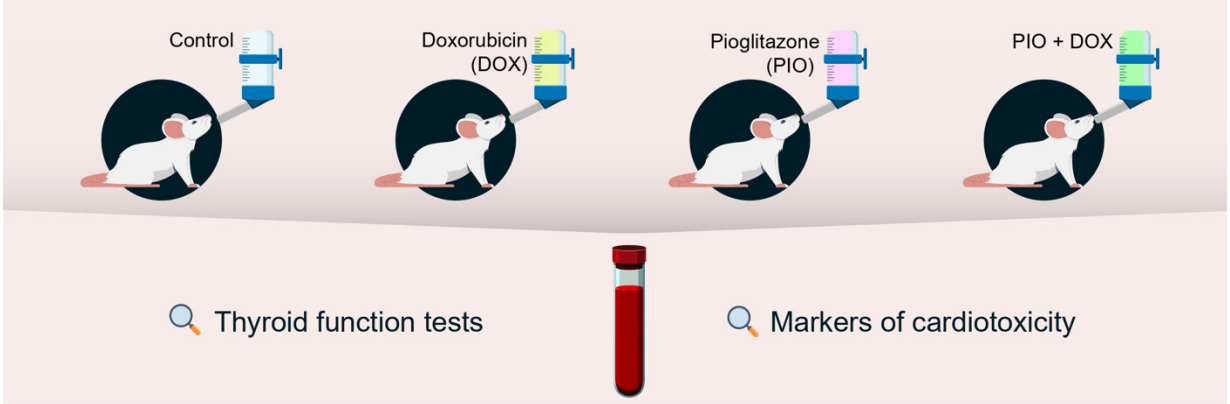
RESULTS: The control and PIO groups did not exhibit significant alterations in any of the examined hormones and markers. In contrast, in the DOX group, T4, FT4, T3, and FT3 levels decreased significantly, whereas troponin I, CK, and CK-MB levels increased significantly, but no significant changes were detected in TSH levels. PIO co-treatment ameliorated these effects of DOX significantly in FT4, FT3, and troponin I.

CONCLUSIONS: PIO may provide protection against hypothyroidism and cardiotoxicity caused by DOX treatment, by significant reversal of FT4, FT3, and troponin I levels.

Key Words:
Chemotherapy, Doxorubicin, Pioglitazone, Hypothyroidism, Cardiotoxicity, Heart disease.

Introduction

Doxorubicin (DOX) is an efficient anticancer medication utilized to treat multiple malignancies, including breast and prostate cancer[1]. The main mechanisms of DOX are a decrease in DNA synthesis induced *via* topoisomerase II inhibition, an increase in the reactive oxygen species (ROS) formation, and the disruption of mitochondrial function[2]. However, despite its efficacy against cancer growth, it has several limitations, including cardiotoxicity, nephrotoxicity, hepatotoxicity, and hypothyroidism[3-6]. Furthermore, recent stud-



Graphical Abstract. Concurrent treatment with PIO reduces DOX-induced hypothyroidism and cardiotoxicity.

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ies in literature have established a link between hypothyroidism and cardiotoxicity following chemotherapy regimens, such as DOX treatment.

Cardiotoxicity can cause blood flow deficiency to the rest of the body, including the brain, and this can result in cerebral hypoxia[7]. Impaired brain oxygenation alters general brain function and also affects the functionality of other organs[8,9]. Accordingly, it has been reported[10] that among patients on DOX treatment who developed cardiac deficiencies, 25-70% also developed cognitive problems. Similarly, hypothyroidism may also have adverse effects on the brain, as neuroimaging research has demonstrated[11] alterations in the hippocampal structure and function of patients with hypothyroidism. In addition, hypothyroidism is characterized by abnormal cardiac function by decreased cardiac contractility[12]. Few investigations[13,14] have focused on the mechanism and etiology of DOX-induced hypothyroidism and cardiotoxicity, or agents that can be employed to protect patients from these toxicities. Therefore, additional research is required to develop new compounds that can reduce the effect of DOX on the thyroid gland and cardiac functions, potentially by improving thyroid hormone release and cardiac outputs.

Pioglitazone (PIO) is a derivative of thiazolidinedione, an anti-diabetic medication, that is used as a selective agonist for peroxisome proliferator-activated receptors (PPARs)[15,16]. Agonism of PPAR improves insulin sensitivity, glucose uptake, and fat metabolism[17]. PIO is currently approved for the therapy of diabetes mellitus, which is associated with insulin resistance[18]. Furthermore, PIO has been reported[19,20] to be a candidate drug for the curing of neurodegeneration such as Alzheimer's and Parkinson's disease, and has also been shown[21,22] to enhance thyroid hormone receptor activation and, thereby, improve thyroid hormone function. In a rat model of hypothyroidism, PIO administration was found[23] to alleviate oxidative stress and memory function. Some studies[24,25] have also reported that PIO can reverse cardiomyopathy induced by type 1 diabetes mellitus. However, one study by Zhong et al[26] has reported the possibility of PIO-inducing cardiomyopathy. Further studies are essential to understand more clearly the impact of PIO- on DOX-induced hypothyroidism and cardiotoxicity and evaluate it as a candidate protective agent against the adverse effects of DOX.

Our prior study[27] assessed the neurotoxic effects of DOX therapy on the function of the brain and investigated the potential ameliorative effect of combining PIO with DOX. The DOX-treated rats exhibited neurotoxicity and cognitive impairment, increased mortality rate, reduced body weight, and elevated neuroinflammation (as indicated by increased IL-1β, TNF-α, and IL-6 levels)[27], and these effects, except for the reduced body weight, were prevented by co-treatment with PIO. These findings demonstrate the beneficial effects of PIO in attenuating DOX-induced neurotoxicity[27] and lay the basis for the present study. Accordingly, the high incidence of hypothyroidism and cardiotoxicity in breast cancer patients and DOX therapy use in breast cancer regimens, limited is identified about DOX effects on female rodents in the development of hypothyroidism and cardiotoxicity after DOX therapy and protection. Therefore, this study examined female rats' DOX-induced hypothyroidism *via* assessing thyroid hormone levels and cardiotoxicity *via* assessing cardiotoxic biomarkers as well as possible PIO protection in female rodents.

Materials and Methods

Chemicals

DOX and pioglitazone hydrochloride (Glados®) were sourced from EBEWE Pharmaceutical Manufacturing located in Attersee, Austria, and Tabuk Pharmaceutical Company located in Tabuk, Saudi Arabia, respectively.

Animals and Drug Administration

Forty Wistar female rats (weighing 150-250 g) were housed individually in plastic cages. The animals were preserved in typical standard laboratory environments under a light and dark cycle for 12 hours each and at 25°C room temperature. They were given free admittance to food and water. The rats were separated into four rat groups (7 in each group): a control group and three different groups treated with DOX, PIO, and DOX+PIO. DOX was intraperitoneally administered at 5 mg/kg dose every three days for twelve days. Thus, the rats in the DOX groups received a complete dose of 20 mg/kg. In the PIO groups, a dose of 2 mg/kg was delivered by dissolving PIO in the drinking water provided to the rats on the same days that DOX was administered. In the control group, rats were administered with saline.

Electrochemiluminescence Immunoassays

On day 14, after the last drug dose was administered, the rats were sacrificed by cervical de-

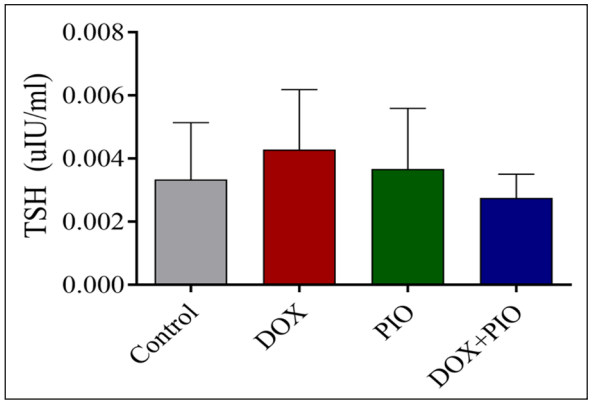

Figure 1. Effects of DOX, PIO, and combination on TSH levels. The graph depicts no significant alterations between the four study rats' groups. The data are presented as SEM for seven animals in each group, analyzed utilizing one-way ANOVA.

capitation after induction of anesthesia with CO_2. Blood was promptly collected into EDTA tubes from the control group, and treated with PIO, DOX, and DOX+PIO groups, and vials containing the blood samples were centrifuged at (12,000 × g) for 10 minutes. The separated plasma was transferred to 2 mL vials and stored at -80°C. Subsequently, the blood samples were analyzed using a fully automated analyzer that utilizes a patented electrochemiluminescence technology for immunoassay analysis of TSH, thyroxine (T4), triiodothyronine (T3), free thyroxine (FT4), free triiodothyronine (FT3), troponin I, creatine kinase (CK), and creatine kinase-myocardial band (CK-MB). The levels of troponin I, CK, and CK-MB are elevated following cardiac infarction, and cardiac toxicity and injury, and they are, therefore, considered as biomarkers of cardiotoxicity[28,29]. The ECL method employed the COBAS INTEGRA 400 plus system according to the manufacturer's directions (Roche Diagnostics GmbH, Mannheim, Germany).

Statistical Analysis

The results of the existing study were analyzed *via* GraphPad Prism 10.0.0.153 (GraphPad, Boston, MA, USA) and were shown as SEM. The ECL results were statistically analyzed using a one-way analysis of variance. Data for each treatment group were compared against the control data. A $p < 0.05$ was counted as demonstrating statistical significance.

Results

TSH Levels Unaffected by DOX or PIO

The results of the ECL analysis indicated that the TSH levels did not significantly vary between the control and three treated groups. Thus, neither the DOX nor the PIO treatments impacted TSH levels (Figure 1).

PIO Reduces DOX Toxic Effects on T4 and FT4 Levels

ECL analysis revealed that the concentrations of T4 and FT4 were noticeably lower in the DOX-treated group compared to the control group. Co-treatment with PIO improved the T4 and FT4 levels, but not significantly (Figures 2A and 2B).

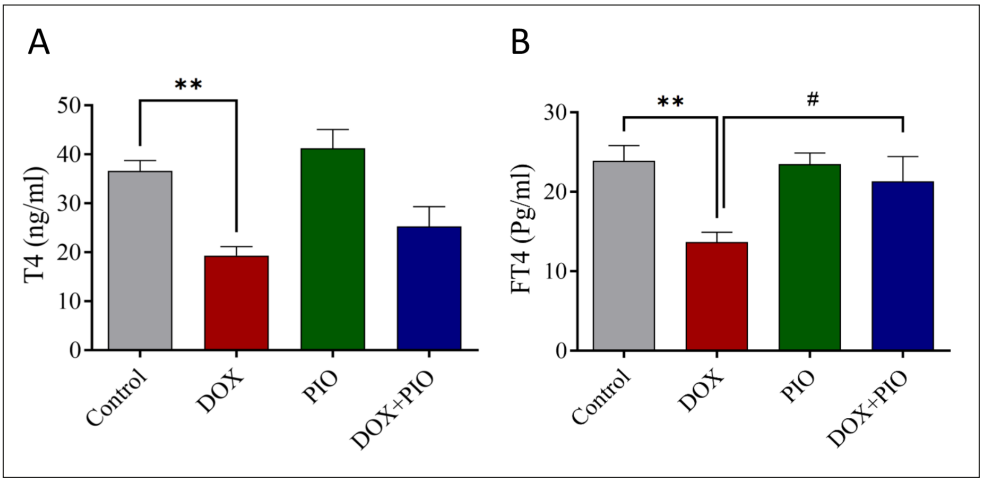

Figure 2. Effects of DOX, PIO, and combination on T4 (**A**) and FT4 (**B**) levels. DOX treatment (20 mg/kg, intraperitoneal injection) caused a significant decrease in the T4 and FT4 levels, but PIO treatment did not affect the T4 and FT4 levels. The DOX+PIO group showed improved T4 and FT4 levels compared to the DOX group. Data are expressed as SEM for seven rats in each rat group. ($^{**}p < 0.01$) and ($^{***}p < 0.001$) related to control rats, and ($^{\#}p < 0.05$) related to DOX rats.

PIO Reduces DOX Toxic Effects on T3 and FT3 Levels

ECL analysis revealed that the concentrations of T3 and FT3 were considerably lower in the DOX group compared to the control group, but the PIO therapy alone did not seem to have a substantial impact on the T3 or FT3 levels, compared to the control group. PIO co-treatment appeared to rescue this effect of DOX, although this effect was not significant (Figures 3A and 3B).

PIO Reduces DOX Toxic Effects on Troponin I Levels

Comparing the DOX-treated rats to the control ones, the troponin I levels were noticeably higher in the DOX-treated rats (*$p < 0.05$) (Figure 4). PIO also appeared to induce an increase in troponin I related to the control rats, but the difference was not statistically significant. PIO+DOX co-treatment led to a reduction, although not significant, in the DOX-induced increase in troponin I.

PIO Reduces DOX Toxic Effects on CK and CK-MB Levels

Compared to the control rats, DOX therapy resulted in a considerable elevation in CK and CK-MB levels. PIO co-treatment restored their levels, but not to a significant extent (*$p < 0.05$) (Figures 5A and 5B).

Discussion

In this present study, the effect of DOX on thyroid and cardiac function was examined in DOX-treated rat models based on measurements of the plasma concentrations of TSH, T4, FT4, T3, FT3, troponin I, CK, and CK-MB. Further, the potential protective effect of PIO (which has been reported[30] to improve thyroid and cardiac function) on DOX-induced hypothyroidism and cardiotoxicity was also investigated.

Previous studies[31,32] have documented that DOX can alter thyroid and cardiac function clinically and experimentally. The results of the existing study are in agreement with these early results, as DOX was found to cause a significant increase in the markers of cardiac toxicity (that is, troponin I, CK, and CK-MB) and a significant decline in the levels of the thyroid hormones assayed. Thyroid hormone receptors are expressed abundantly in the brain and heart[33,34], and a reduction in thyroid hormones can affect the activities of these receptors and subsequently lead to altered heart and brain function[35,36]. Accordingly, hypothyroidism has been reported[12,37] to cause cardiac deficiency and mental problems. In addition, alterations in cardiac function have been found[38] to reduce blood flow and affect the blood supply to the rest of the body, including the brain, and cardiac deficiency has also been associated[39] with hypothyroidism. Thus, the pathways *via* which DOX affected cardiac and thyroid function may be related; therefore, they need to be investigated in more detail, as they may help identify potential therapeutic agents that can prevent or ameliorate these adverse effects of DOX. The current study investigated TSH, T4, FT4, T3, and FT3 levels after treatment with DOX, PIO, and a combination of DOX+PIO. Interestingly, the results indicated

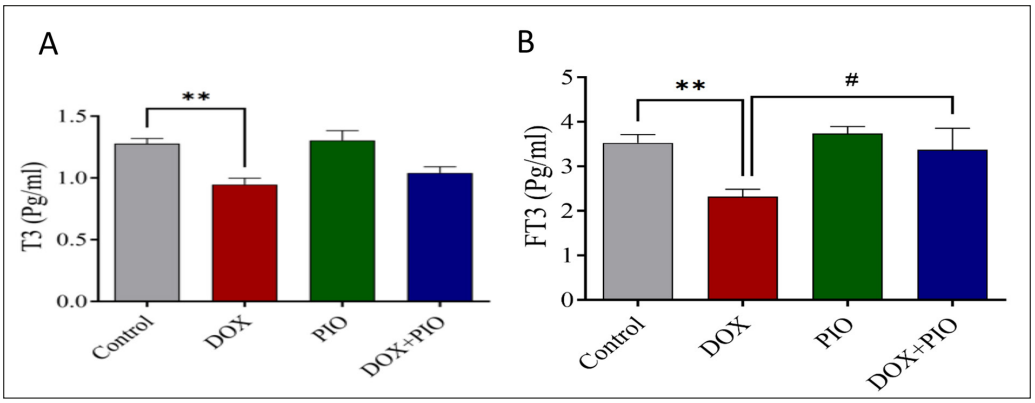

Figure 3. Effects of DOX, PIO, and combination on T3 (**A**) and FT3 (**B**) levels. DOX treatment (20 mg/kg, intraperitoneal injection) significantly decreased the T3 and FT3 levels related to the control group, but PIO treatment did not alter the T3 and FT3 levels. DOX+PIO co-treatment showed improved T3 and FT3 levels compared to the DOX-only treatment, but this effect was not significant. The expression of data is as SEM for seven rats in each rat group. (**$p < 0.01$) and (***$p < 0.001$) related to the control rats, and (#$p < 0.05$) related to DOX rats.

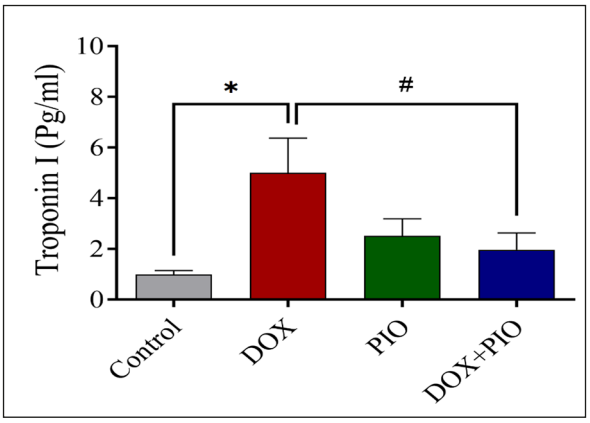

Figure 4. Effects of DOX, PIO, and combination on troponin I levels. DOX treatment (20 mg/kg, intraperitoneal injection) led to a noticeable elevation in troponin I levels related to control group. PIO treatment also led to an increase in troponin I levels, but it was not significant. DOX+PIO co-treatment counteracted the increase induced by DOX, but not significantly. The expression of data was as SEM for seven rats in each rat group. ($^{*}p < 0.05$) related to the control rats, and ($^{\#}p < 0.05$) related to DOX rats.

no significant alterations in TSH levels following DOX or PIO treatments in all groups. Further, the T4, FT4, T3, and FT3 levels were notably decreased in the DOX-treated rats, but PIO did not cause any significant changes. That is, while PIO co-treatment was found to lead to an improvement in the circulating levels of T4, T3, FT4, and FT3, the observed effect was not significant in T4 and T, while there was a notable improvement in FT4 and FT3. A study[36] on type 2 diabetes patients reported that PIO led to a notable decline in FT4 levels and a notable elevation in TSH levels. Thus, the present findings need to be explored further through more studies in order to confirm whether PIO does indeed have any ameliorative effect on DOX-induced thyroid toxicity.

The results of this study established the cardiotoxic effects of DOX based on significantly increased levels of troponin I, CK, and CK-MB related to the control group. Further, PIO was found to reverse these effects significantly in troponin I, but not to a significant extent in the CK and CK-MB levels. Nonetheless, similar beneficial effects of PIO have been reported[30,40] previously. For example, one study[40] in a mouse model showed that PIO could reverse DOX-induced cardiotoxicity. Further, a study[30] on individuals with type 2 diabetes mellitus found that PIO could improve cardiac function. However, these findings need further verification, as PIO has also been reported[41] to aggravate DOX-induced cardiomyopathy.

Limitations

The present findings are limited by its *in vivo* design. The findings need to be confirmed in *in vitro* experiments and clinical trials in the future. In addition, we were unable to examine the mechanistic details underlying the impacts of DOX and PIO on thyroid and cardiac function. For example, a previous study[25] on a rat model reported that PIO could alleviate diabetic cardiomyopathy by suppressing cardiac CaMKII/NF-κB signaling and enhancing PPAR-γ expression. With regard to its effect on thyroid function, it would be fascinating to investigate the potential role of thyroid

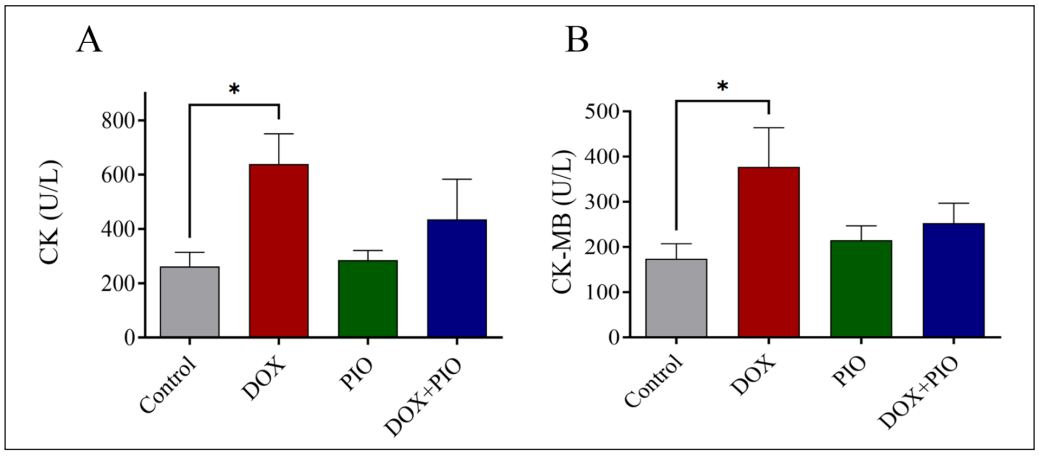

Figure 5. Effects of DOX, PIO, and combination on CK (A) and CK-MB (B) levels. DOX treatment (20 mg/kg, intraperitoneal administration) led to a noticeable elevation in the CK and CK-MB levels that was reversed by DOX+PIO co-treatment (although not significantly). The expression of data was as SEM for seven in each rats group, and one-way ANOVA made comparisons with control rats. ($^{*}p < 0.05$) related to control rats.

hormone receptors, particularly THRα1, which is principally found in the cardiac and skeletal muscle, and THRβ1, which is predominantly found in the hepatic, kidneys, and brain[42].

Conclusions

Our results confirm previous findings that DOX treatment can induce hypothyroidism and cardiotoxicity and indicate that PIO may provide protection against these DOX-induced toxicities in rat models. These findings need to be verified through further studies that also investigate the related mechanisms, as they may hold the potential for future therapeutic strategies against DOX-induced toxicities.

Conflict of Interest
The authors declare that they have no conflict of interests.

Informed Consent
Not applicable.

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This study was not funded by any external sources.

Ethics Approval
This research was permitted by the Institutional Animal Care of the College of Pharmacy and Scientific Research Deanship at Qassim University (Number Issue 22-16-02).

Availability of Data and Materials
The corresponding author can provide the study data upon request.

References

1) Thorn CF, Oshiro C, Marsh S, Hernandez-Boussard T, McLeod H, Klein TE, Altman RB. Doxorubicin pathways. Pharmacogenet Genomics 2011; 21: 440-446.
2) Alhowail A, Almogbel Y. Metformin administration increases the survival rate of doxorubicin-treated mice. Pharmazie 2019; 74: 737-739.
3) Song S, Chu L, Liang H, Chen J, Liang J, Huang Z, Zhang B, Chen X. Protective Effects of Dioscin Against Doxorubicin-Induced Hepatotoxicity Via Regulation of Sirt1/FOXO1/NF-κb Signal. Front Pharmacol 2019; 10: 1030.
4) Zhao L, Zhang B. Doxorubicin induces cardiotoxicity through upregulation of death receptors mediated apoptosis in cardiomyocytes. Sci Rep 2017; 7: 44735.
5) Afsar T, Razak S, Almajwal A, Al-Disi D. Doxorubicin-induced alterations in kidney functioning, oxidative stress, DNA damage, and renal tissue morphology; Improvement by Acacia hydaspica tannin-rich ethyl acetate fraction. Saudi J Biol Sci 2020; 27: 2251-2260.
6) Alharbi I, Alharbi H, Almogbel Y, Alalwan A, Alhowail A. Effect of Metformin on Doxorubicin-Induced Memory Dysfunction. Brain Sci 2020; 10: 152.
7) Allen KA, Brandon DH. Hypoxic Ischemic Encephalopathy: Pathophysiology and Experimental Treatments. Newborn Infant Nurs Rev 2011; 11: 125-133.
8) Watts ME, Pocock R, Claudianos C. Brain Energy and Oxygen Metabolism: Emerging Role in Normal Function and Disease. Front Mol Neurosci 2018; 11: 216.
9) Sandroni C, Cronberg T, Sekhon M. Brain injury after cardiac arrest: pathophysiology, treatment, and prognosis. Intensive Care Med 2021; 47: 1393-1414.
10) Volkova M, Russell R. Anthracycline Cardiotoxicity: Prevalence, Pathogenesis and Treatment. Curr Cardiol Rev 2012; 7: 214-220.
11) Cooke GE, Mullally S, Correia N, O'Mara SM, Gibney J. Hippocampal Volume Is Decreased in Adults with Hypothyroidism. Thyroid 2014; 24: 433-440.
12) Yamakawa H, Kato TS, Noh JY, Yuasa S, Kawamura A, Fukuda K, Aizawa Y. Thyroid Hormone Plays an Important Role in Cardiac Function: From Bench to Bedside. Front Physiol 2021; 12: 606931.
13) Kong CY, Guo Z, Song P, Zhang X, Yuan YP, Teng T, Yan L, Tang QZ. Underlying the Mechanisms of Doxorubicin-Induced Acute Cardiotoxicity: Oxidative Stress and Cell Death. Int J Biol Sci 2022; 18: 760-770.
14) Bhagat A, Shrestha P, Jeyabal P, Peng Z, Watowich SS, Kleinerman ES. Doxorubicin-induced cardiotoxicity is mediated by neutrophils through release of neutrophil elastase. Front Oncol 2022; 12: 947604.
15) Hong F, Pan S, Guo Y, Xu P, Zhai Y. PPARs as Nuclear Receptors for Nutrient and Energy Metabolism. Molecules 2019; 24: 2545.
16) Villacorta L, Schopfer Francisco J, Zhang J, Freeman Bruce A, Chen YE. PPARγ and its ligands: therapeutic implications in cardiovascular disease. Clin Sci (Lond) 2009; 116: 205-218.
17) Leonardini A, Laviola L, Perrini S, Natalicchio A, Giorgino F. Cross-Talk between PPARγand Insulin Signaling and Modulation of Insulin Sensitivity. PPAR Research 2009; 2009: 1-12.

18) Qian X, Wang H, Yang G, Gao Z, Luo Y, Dong A, Zhang F, Xu M, Liu S, Yang X, Chen Y, Li G. Pioglitazone Improved Insulin Sensitivity and First Phase Insulin Secretion Among Obese and Lean People with Diabetes: A Multicenter Clamp Study. Diabetes Ther 2018; 9: 815-826.

19) Chang KL, Pee HN, Yang S, Ho PC. Influence of drug transporters and stereoselectivity on the brain penetration of pioglitazone as a potential medicine against Alzheimer's disease. Sci Rep 2015; 5: 9000.

20) Takechi R, Lam V, Brook E, Giles C, Fimognari N, Mooranian A, Al-Salami H, Coulson SH, Nesbit M, Mamo JCL. Blood-Brain Barrier Dysfunction Precedes Cognitive Decline and Neurodegeneration in Diabetic Insulin Resistant Mouse Model: An Implication for Causal Link. Front Aging Neurosci 2017; 9: 399.

21) Saunders AM, Burns DK, Gottschalk WK. Reassessment of Pioglitazone for Alzheimer's Disease. Front Neurosci 2021; 15: 666958.

22) Alhowail A, Alsikhan R, Alsaud M, Aldubayan M, Rabbani SI. Protective Effects of Pioglitazone on Cognitive Impairment and the Underlying Mechanisms: A Review of Literature. Drug Des Devel Ther 2022; 16: 2919-2931.

23) Baghcheghi Y, Salmani H, Beheshti F, Shafei MN, Sadeghnia HR, Soukhtanloo M, Ebrahimzadeh Bideskan A, Hosseini M. Effects of PPAR-γ agonist, pioglitazone on brain tissues oxidative damage and learning and memory impairment in juvenile hypothyroid rats. Int J Neurosci 2019; 129: 1024-1038.

24) Mannucci E, Giaccari A, Gallo M, Targher G, Pintaudi B, Candido R, Monami M. Effects of pioglitazone on cardiovascular events and all-cause mortality in patients with type 2 diabetes: A meta-analysis of randomized controlled trials. Nutr Metab Cardiovasc Dis 2022; 32: 529-536.

25) Gbr AA, Abdel Baky NA, Mohamed EA, Zaky HS. Cardioprotective effect of pioglitazone and curcumin against diabetic cardiomyopathy in type 1 diabetes mellitus: impact on CaMKII/NF-κB/TGF-β1 and PPAR-γ signaling pathway. Naunyn Schmiedebergs Arch Pharmacol 2020; 394: 349-360.

26) Zhong W, Jin W, Xu S, Wu Y, Luo S, Liang M, Chen L. Pioglitazone Induces Cardiomyocyte Apoptosis and Inhibits Cardiomyocyte Hypertrophy Via VEGFR-2 Signaling Pathway. Arq Bras Cardiol 2018; 111: 162-169.

27) Alsaud MM, Alhowail AH, Aldubayan MA, Almami IS. The Ameliorative Effect of Pioglitazone against Neuroinflammation Caused by Doxorubicin in Rats. Molecules 2023; 28: 4775.

28) Ottlinger ME, Pearsall L, Rifai N, Lipshultz SE. New developments in the biochemical assessment of myocardial injury in children: troponins T and I as highly sensitive and specific markers of myocardial injury. Progress in Pediatric Cardiology 1997; 8: 71-81.

29) Babuin L. Troponin: the biomarker of choice for the detection of cardiac injury. CMAJ 2005; 173: 1191-1202.

30) van der Meer RW, Rijzewijk LJ, de Jong HWAM, Lamb HJ, Lubberink M, Romijn JA, Bax JJ, de Roos A, Kamp O, Paulus WJ, Heine RJ, Lammertsma AA, Smit JWA, Diamant M. Pioglitazone Improves Cardiac Function and Alters Myocardial Substrate Metabolism Without Affecting Cardiac Triglyceride Accumulation and High-Energy Phosphate Metabolism in Patients With Well-Controlled Type 2 Diabetes Mellitus. Circulation 2009; 119: 2069-2077.

31) Cappola AR, Desai AS, Medici M, Cooper LS, Egan D, Sopko G, Fishman GI, Goldman S, Cooper DS, Mora S, Kudenchuk PJ, Hollenberg AN, McDonald CL, Ladenson PW, Celi FS, Dillman W, Ellervik C, Gerdes AM, Ho C, Iervasi G, Lerman A, Makino A, Ojamaa K, Peeters R, Pingitore A, Razvi S, Wassner AJ. Thyroid and Cardiovascular Disease. Circulation 2019; 139: 2892-2909.

32) de Groot S, Janssen LGM, Charehbili A, Dijkgraaf EM, Smit VTHBM, Kessels LW, van Bochove A, van Laarhoven HWM, Meershoek-Klein Kranenbarg E, van Leeuwen-Stok AE, van de Velde CJH, Putter H, Nortier JWR, van der Hoeven JJM, Pijl H, Kroep JR. Thyroid function alters during neoadjuvant chemotherapy in breast cancer patients: results from the NEOZOTAC trial (BOOG 2010-01). Breast Cancer Res Treat 2015; 149: 461-466.

33) Saponaro F, Sestito S, Runfola M, Rapposelli S, Chiellini G. Selective Thyroid Hormone Receptor-Beta (TRβ) Agonists: New Perspectives for the Treatment of Metabolic and Neurodegenerative Disorders. Front Med (Lausanne) 2020; 7: 331.

34) Sahin L, Keloglan Müsüroglu S, Selin Cevik O, Cevik K, Orekici Temel G. Hyperthyroidism leads learning and memory impairment possibly via GRIN2B expression alterations. Brain Res 2023; 1802: 148209.

35) Vallortigara J, Chassande O, Higueret P, Enderlin V. Thyroid Hormone Receptor Alpha Plays an Essential Role in the Normalisation of Adult-Onset Hypothyroidism-Related Hypoexpression of Synaptic Plasticity Target Genes in Striatum. J Neuroendocrinol 2009; 21: 49-56.

36) van Vliet NA, van Heemst D, Almeida OP, Åsvold BO, Aubert CE, Bae JB, Barnes LE, Bauer DC, Blauw GJ, Brayne C, Cappola AR, Ceresini G, Comijs HC, Dartigues J-F, Degryse J-M, Dullaart RPF, van Eersel MEA, den Elzen WPJ, Ferrucci L, Fink HA, Flicker L, Grabe HJ, Han JW, Helmer C, Huisman M, Ikram MA, Imaizumi M, de Jongh RT, Jukema JW, Kim KW, Kuller LH, Lopez OL, Mooijaart SP, Moon JH, Moutzouri E, Nauck M, Parle J, Peeters RP, Samuels MH, Schmidt CO, Schminke U, Slagboom PE, Stordal E, Vaes B, Völzke H, Westendorp RGJ, Yamada M, Yeap BB, Rodondi N, Gussekloo J, Trompet S. Association of Thyroid Dysfunction With Cognitive Function. JAMA Intern Med 2021; 181: 1440-1450.

37) Heinrich TW, Grahm G. Hypothyroidism Presenting as Psychosis: Myxedema Madness Revisited. Prim Care Companion J Clin Psychiatry 2003; 5: 260-266.

38) Xu C, Tao X, Ma X, Zhao R, Cao Z, Morishita R. Cognitive Dysfunction after Heart Disease: A Manifestation of the Heart-Brain Axis. Oxid Med Cell Longev 2021; 2021: 1-10.

39) Kannan L, Shaw PA, Morley MP, Brandimarto J, Fang JC, Sweitzer NK, Cappola TP, Cappola AR. Thyroid Dysfunction in Heart Failure and Cardiovascular Outcomes. Circ Heart Fail 2018; 11: e005266.

40) Pakravan G, Peymani M, Abedpoor N, Safaeinejad Z, Yadegari M, Derakhshan M, Nasr Esfahani MH, Ghaedi K. Antiapoptotic and anti-inflammatory effects of Pparγ agonist, pioglitazone, reversed Dox-induced cardiotoxicity through mediating of miR-130a downregulation in C57BL/6 mice. J Biochem Mol Toxicol 2022; 36: e23041.

41) Saraogi P, Pillai KK, Singh BK, Dubey K. Rosiglitazone and pioglitazone aggravate doxorubicin-induced cardiomyopathy in Wistar rats. Biomedicine & Aging Pathology 2011; 1: 65-71.

42) Wallis K, Dudazy S, Hogerlinden Mv, Nordström K, Mittag J, Vennström Br. The Thyroid Hormone Receptor α1 Protein Is Expressed in Embryonic Postmitotic Neurons and Persists in Most Adult Neurons. Mol Endocrinol 2010; 24: 1904-1916.