Assessment of Lithium-Induced Cardiotoxicity in Rats and the Potential Effect of Selenium: Sub-Chronic Study

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KEYWORDS
Lithium,
Cardiotoxicity,
Selenium,
Oxidative stress,
Apoptosis.

ABSTRACT

Lithium salts are used in treating many neurotic and psychosomatic disorders. Studying the toxic effects of this medication is necessary because doctors commonly keep their patients on long-term lithium treatment. The goal of the current study was to assess the cardiotoxic effect of lithium on adult Wistar albino rats and the possible roles of oxidative stress and apoptosis and also to assess the protective effect of selenium. Twenty-four adult male Wistar albino rats were divided into four equal groups; control, selenium-treated group; received 0.2 mg/kg/d dissolved in distilled water, lithium-treated group; received 53 mg/kg/day of lithium carbonate dissolved in 1 ml 0.9% sodium chloride orally by gavage, and lithium-and-selenium treated group received lithium and selenium in the previous doses. After 90 days, we demonstrated that rats received lithium (53 mg/kg/day) demonstrated a significantly higher malondialdehyde (MDA) level and a significantly lower glutathione (GSH) level compared to controls indicating induction of oxidative stress in the cardiac tissues. In addition, there was a marked rise in cardiac biomarker cardiac troponin I (cTnI) level. The immunohistochemistry examination of the heart for caspase3 expression revealed a significant increase in the lithium group in comparison with the control. These results suggest that lithium-induced cardiotoxicity in rats is due to oxidative stress & apoptosis. Selenium administration significantly mitigated lithium's cardiotoxic effects. It can be used to alleviate the cardiotoxic effects of lithium.

Introduction

Lithium is commonly utilized in the treatment of mania and other mental diseases and is frequently used for a long time (Shah et al., 2015). Lithium use for an extended period at therapeutic doses may result in problems like neurotoxicity (Chen et al., 2004), nephrotoxicity, infertility, and impaired thyroid function (Henry, 2002).

The heart is becoming a more significant target for a wide range of hazardous agents, such as environmental pollutants, chemicals, and medications (Jokinen et al., 2011). However, there has been little research on the toxic effects of lithium carbonate on cardiac tissue (Nciri et al., 2008). Lithium can cause many cardiotoxic side effects, including dysrhythmias, cardio-myopathy, and even acute myocardial infarction (Asim et al., 2016). Also, Shah et al. (2015) reported that albino rat hearts, after receiving therapeutic doses of lithium, revealed degeneration of cardiomyocytes resulting in necrosis, fibrosis, sub-endocardial haemorrhages and myocarditis. They advocated that the patient receiving prolonged

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lithium therapy must be monitored for its adverse cardiac effects.

Efrati et al. (2005) and Nciri et al. (2012) proposed that oxidative damage plays a role in the cardiotoxicity of lithium. It has been suggested that reactive oxygen species (ROS) may influence apoptosis (Yu et al., 2006) as a result of loss of membrane potential and activation of caspase 3 to start the apoptotic destruction of cardiomyocytes (Suchal et al., 2016). Cardiovascular diseases include atherosclerosis; hypertension, heart failure, and hypertrophy are all impacted by oxidative stress (Kattoor et al., 2017).

One of the necessary trace elements is selenium, which plays an antioxidant role in both humans and animals as it can scavenge free radicals and also controls cellular redox homeostasis (Diwakar et al., 2017). According to Özsobaci et al. (2018) selenium has been demonstrated to protect against oxidative damage and apoptosis through the mitochondrial pathway.

The present work aims to study the cardiotoxic effects of lithium on adult male rats and the oxidative damage and Caspase 3 expression in the heart of lithium-treated Wistar albino rats and the potential ameliorative effect of selenium supplementation.

Materials and method:

Chemicals

Lithium carbonate (white crystalline powder) was obtained from Sigma–Aldrich Inc., Egypt. The required doses were dissolved in 0.9% NaCl and given by oral gavage. Active caspase-3 immunostain (rabbit polyclonal antibodies) was purchased from Servicebio, China. Selenium in the form of powder was purchased from Sigma–Aldrich Inc., Egypt.

Animals

Male Wistar albino rats (150 g- 200 g) were obtained from an experimental animal house, Faculty of Pharmacy, Kafrelsheikh University, Egypt. Rats were maintained under standard environmental conditions at a temperature of 22°C ± 2°C, 12 h light/dark cycle, 41% - 55% relative humidity, and provided with food and free water throughout the experimental period. The rats underwent acclimatization to laboratory conditions for 7 days before starting the experiment. All experimental animals in this study were handled following the Guide for the Care and Use of Laboratory Animals (Vasbinder and Locke, 2016).

Ethical consideration

In the current study, we followed the ethical guidelines according to the ethical norms approved by the Scientific Research Ethics Committee, Faculty of Medicine, Kafrelsheikh University (code: MKSU 50-6-12).

Experimental Design:

The study was conducted on 24 rats which were distributed into 4 equal groups (6 rats each). The study duration was 90 days (sub-chronic study). Rats were randomly divided into 4 groups:

- Group I (control group): 6 untreated rats served as control, received 0.9% NaCl by oral gavage for 90 days.
- Group II (selenium-treated group): 6 rats received a selenium dose of 0.2 mg/kg/d dissolved in 1 ml 0.9% NaCl for 90 days (Yu et al., 2006).
- Group III (lithium-treated rats): 6 rats received 53 mg/kg/d of lithium carbonate (approximately 1/10 of LD50 of 525 mg/kg) dissolved in 1 ml 0.9% NaCl and given once by oral gavage for 90 days (Abdel Hamid et al., 2020).

- Group IV (lithium and selenium treated group): 6 rats received the same lithium dose in group II and the same selenium dose as in group III for 90 days.

Dose calculation:

Lithium dose underwent calculation by converting adult human therapeutic dose (up to 2400 mg/day) (Horton et al., 2012) to animal dose utilizing the following equation:

Animal equivalent dose (AED) (mg / kg) = Human does (mg / kg) × Km ratio (Nair and Jacob, 2016). The calculated dose of lithium was 53 mg/kg/day of the weight of rats based on the maximum therapeutic daily lithium dose in humans (this calculated dose is approximately 1/10 of LD50 of 525 mg/kg).

Biochemical analysis:

Assessment of cardiotoxicity index:

Heparinized blood samples (1 mL) were drawn by retro-orbital plexus from the anaesthetized animals using a capillary glass tube. Centrifuging the blood at 3000 rpm for 10 minutes separated the serum from the collected blood, which was then kept at (-20) C^o for subsequent quantification of cardiac troponin I (cTnI). A quantitative immuno-enzymometric test for cardiac troponin I (CTnI) in rat serum was performed (Hammadi et al., 2015).

Assessment of apoptosis:

The hearts of the sacrificed rats underwent dissection immediately and fixed in 10 % neutral buffered formalin for immunohistochemistry examination (caspase3) according to Hamed et al. (2020).

Assessment of oxidative stress markers:

Levels of glutathione (GSH) and malondialdehyde (MDA) were measured in the cardiac tissue homogenates using commercially available kits.

Statistical analysis and data interpretation:

Data were analyzed using the Statistical Package of Social Science (SPSS) program for Windows (Standard version 22). The normality of data was first tested with the Shapiro test. Data were expressed as mean± standard deviation (SD). ANOVA test was used to compare more than two means. The differences in mean values were considered statistically significant at $p<0.05$.

Results:

There were no deaths among the rats during the study duratuion. The cardiac troponin I (cTnI) level in the four animal groups is presented in table (1). There was a significant increase in cTnI level in the lithium group compared to the control and a significant decrease in cTnI level in rats treated with selenium together with lithium compared to the group that received lithium alone. A non-statistically significant difference was found between the control and selenium groups.

Table (1): Cardiac troponin I level (ng/ml) in Wistar albino rats following lithium and selenium administration.

Parameter	Group 1 (Control)	Group 2 (Selenium)	Group 3 (Lithium)	Group 4 (Selenium +Lithium)	Test of significance between the groups
cTnI level (ng/ml)	0.63 ± 0.05	0.57± 0.02	5.50 ± 0.52	2.16 ± 0.31	p1<0.001* p2<0.001* p3<0.001* p4=0.989 p5<0.001* p6<0.001*

Used test: One Way ANOVA test *statistically significant if p<0.05. Parameters were expressed as mean±SD. cTnI: cardiac troponin I. P1: the difference between selenium and lithium groups, P2: the difference between selenium and selenium + lithium groups, P3: the difference between lithium and selenium + lithium groups, P4: the difference between selenium and control groups, P5: the difference between lithium and control groups, P6: the difference between selenium + lithium and control groups.

As presented in table (2); oxidative damage in cardiac tissues was assessed by measuring MDA and GSH levels in the four animal groups. Oral feeding of lithium induced a significant increase in MDA level compared to the control group and a significant decrease in GSH level in the lithium group compared to the control. Administration of selenium together with lithium caused a significant decrease in MDA level compared to the lithium group and a significant increase in GSH level compared to that receiving lithium alone.

Table (2): Malondialdehyde (MDA) and glutathione (GSH) levels in Wistar albino rats following lithium and selenium administration.

Parameters	Group 1 (Control)	Group 2 (Selenium)	Group 3 (Lithium)	Group 4 (Selenium + Lithium)	Test of significance between groups
MDA (nmol/g.tissue)	14.40 ± 0.30	13.65 ± 0.67	34.28 ± 6.18	22.90 ± 2.26	p1<0.001* p2=0.001* p3<0.001* p4=0.979 p5<0.001* p6=0.001*
GSH (mmol/g.tisse)	2.12 ± 0.17	2.22 ± 0.18	0.58 ± 0.08	1.33 ± 0.35	p1<0.001* p2<0.001* p3<0.001* p4=0.858 p5<0.001* p6<0.001*

Used test: One Way ANOVA test *statistically significant if p<0.05. Parameter expressed as mean±SD. MDA: Malondialdehyde, GSH: glutathione. P1: the difference between selenium and lithium groups, P2: the difference between selenium and selenium + lithium groups, P3: the difference between lithium and selenium + lithium groups, P4: the difference between selenium and control groups, P5: the difference between lithium and control groups, P6: the difference between selenium + lithium and control groups.

The apoptotic tissue injury was evaluated by the immunohistochemical examination of the proapoptotic marker caspase 3. The immunohistochemistry examination of caspase 3 in cardiac slices is shown in figure (1). It showed almost negative immunostaining for Caspase 3 expression in the control and selenium groups' cardiac muscle, while it is significantly elevated in the lithium group as evidenced by the intensive brownish staining, and decreased in the lithium pluse selenium group.

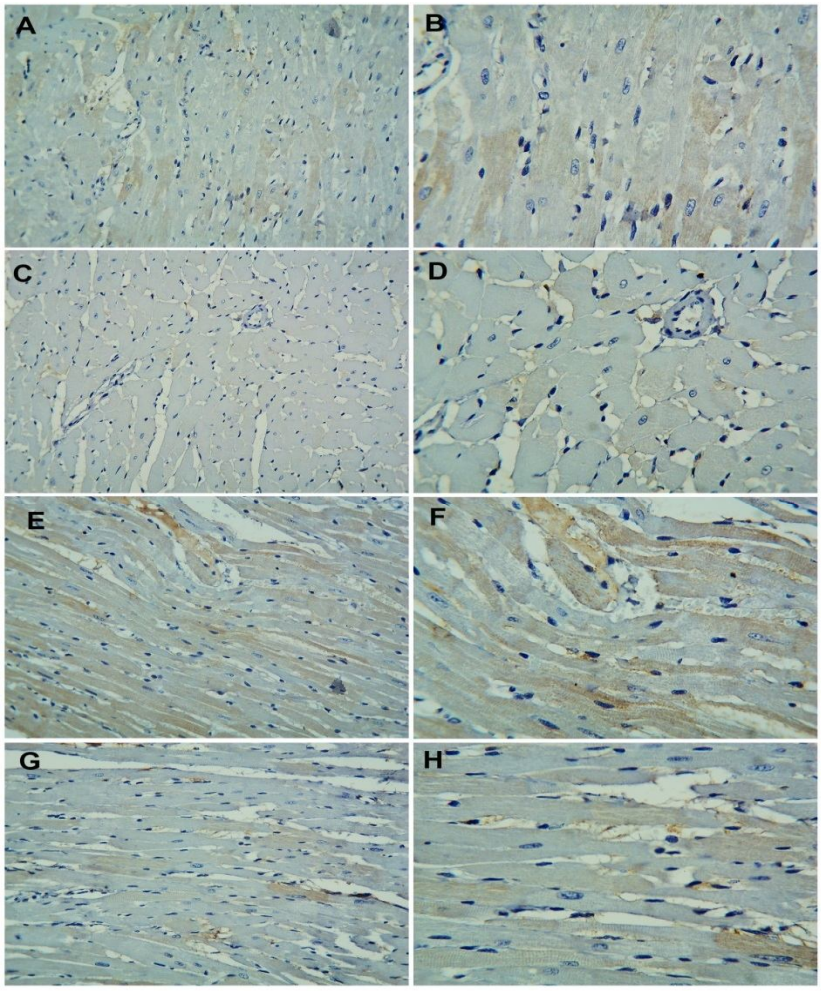

Fig.(1): Histopathological sections in the rats' hearts stained with Caspase-3 immune stain. A & B is the control group, C & D is the selenium group, E & F is the lithium group, and G & H is the lithium + selenium group. The cardiac muscle of the control and the selenium groups show minimal expression. The expression of the color is notably increased in the lithium group and decreased in the lithium plus selenium group. (Caspase-3 immune stain; A, C, E , G X 200& B, D, F, H X 400).

Figure (2) represents quantitative image analysis for caspase 3 staining. Caspase 3 expression was significantly elevated ($p < 0.05$) in the lithium-treated rats in comparison with controls while it was significantly decreased ($p < 0.05$) in the lithium plus selenium group compared to the lithium group.

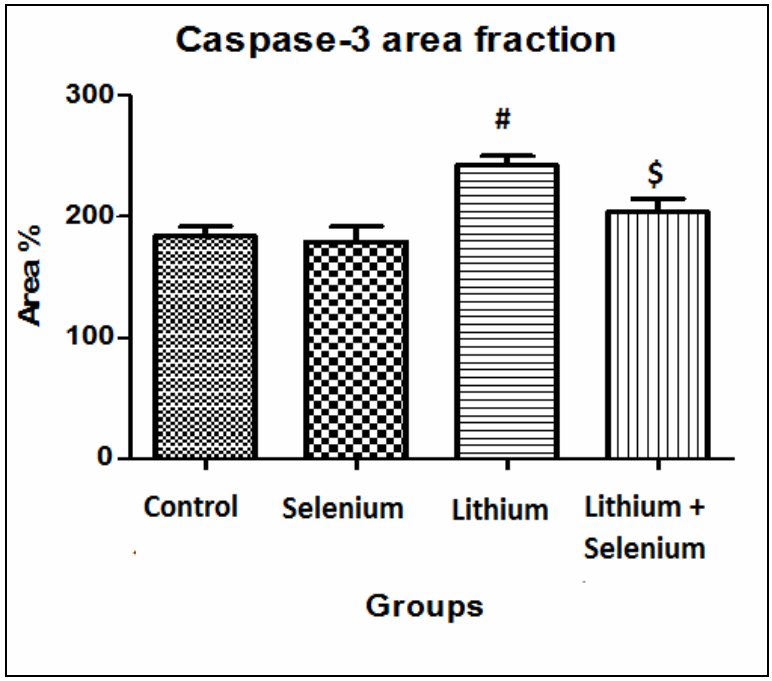

Fig. (2): Quantitative image analysis for caspase 3 immunohistochemical staining expressed as optical densities. Data are presented as mean; #: significantly different from control group while $ significantly different from lithium group at $p < 0.05$ using one-way ANOVA followed by Tukey as post hoc test.

Discussion:

One of the most potent and frequently prescribed drugs for the treatment of numerous mental conditions, including bipolar disorder, is lithium. But it has a small therapeutic index and toxic effects on many tissues. The goal of the current research was to study the cardiotoxicity induced by lithium in male rats and the potential molecular mechanisms through studying its association with oxidative damage and apoptosis as well as how selenium was able to counteract this toxic effect.

The findings of our study showed that lithium induced myocardial damage as evidenced by a significant elevation in cTnI level in the lithium group in comparison to controls and a significant decrease in cTnI level in rats treated with selenium together with lithium compared to the group received lithium alone. The significant increase in cTnI in lithium-treated rats further supported cardiomyocyte damage. Injury to cardiac muscle fibers causes the release of cTnI due to intramyocardial proteolysis (Feng et al., 2001). Myocardial injury caused by lithium was confirmed by the evaluation of cTnI level which showed significantly elevated levels.

This is in accordance with Abdel Hamid et al. (2020), who reported that cTnI was significantly greater in rats receiving lithium in comparison to control. Moreover, they reported histopathological changes including separation between cells, hyalinization with disarranged, degenerated cardiac fibers containing pyknotic nuclei, and cellular aggregates. Shah et al. (2015) reported degenerative changes in cardiomyocytes in rats receiving lithium for 12 weeks in the form of separation of myocardial fibers with inflammatory cells, oedema, myocardial necrosis, and subendocardial and myocardial haemorrhages indicating the presence of significant cell damage.

Our work revealed a significant rise in MDA concentration and decreased GSH concentrations in rats received lithium alone which may be due to oxidative stress induced by lithium while rats treated with selenium together with lithium showed a significant reduction in MDA and a significant rise in GSH concentration compared to that receiving lithium alone. Based on these findings, the cardiotoxicity caused by lithium can be linked to oxidative damage.

In a study by Mezni et al. (2017), it was revealed that lithium-induced oxidative damage in rats' cardiac tissues was evidenced by a rise in the intracellular levels of hydrogen peroxide. In a prior study by Vijaimohan et al. (2010), lithium was associated with causing oxidative stress and oxidative DNA damage and so lead to oxidative damage to the rat cardiac tissues.

The apoptotic cardiac injury caused by lithium was evaluated by the immuno-histochemical examination of the proapoptotic marker caspase 3. Lithium caused apoptotic cell death in the cardiac tissue by increasing the expression of caspase 3. The immunohistochemistry examination of caspase 3 in cardiac slices revealed that caspase 3 expression is minimal in the control and selenium groups' cardiac muscle, while it is significantly elevated in the lithium group and decreased in the lithium + selenium group. In contrast, treatment of rats with selenium ameliorated the apoptotic effects of lithium as evidenced by down-regulating caspase 3 expression.

Abdel Hamid et al. (2020) demonstrated that lithium was associated with cardiomyocyte apoptosis as was evidenced by a significant overexpression of miRNA-1, miR-21, and miR-29b in the lithium-treated group which are related to apoptosis of cardiomyocytes.

Shen et al. (2020) found that human cardiomyocytes were damaged by lithium. It can not only reduce cardiomyocyte function but also increase cardiomyocyte apoptosis.

Lithium-associated cardiotoxic effects were greatly alleviated by selenium co-treatment in group IV as seen by significantly decreased cTnI level, significantly decreased MDA, and significantly increased GSH level and lower caspase 3 expression in cardiomyocytes in comparison to lithium-received rats.

Through modification of the p38 MAPK and nuclear factor kappaB (NF-B) signaling pathways, selenium can reduce oxidative stress responses (Kim et al., 2004). Due to the inhibition of ASK1/JNK and the activation of the PI3-K/Akt pathway, selenite prevents hydrogen peroxide from inducing cell apoptosis. It also modulates the mammalian mitogen-activated protein kinase pathways and downregulates the JNK/SAPK signaling pathway through the inhibition of JNK/SAPK through a thiol redox mechanism (Yoon et al., 2002& Park et al., 2000).

Several studies demonstrated that selenium has anti-apoptosis properties (Brozmanová et al., 2010; Yüksel et al., 2017; Defo Deeh et al., 2019).

In conclusion, the findings of this study suggest that lithium induces cardiotoxicity in rats. One of the possible mechanisms of lithium-induced cardiotoxicity may be due to oxidative stress and caspase 3 activation. Selenium can improve lithium-induced cardiac injury.

Because lithium salts have a narrow therapeutic/toxic ratio, therefore, it is advised that individuals receiving this medication be carefully monitored for developing cardiac problems.

Conflict of interest:

The authors declare that they have no conflicts of interest in this research.

References:

Abdel Hamid, O.I., Ibrahim, E.M., Hussien, M.H., et al. (2020). ´The molecular mechanisms of lithium-induced cardiotoxicity in male rats and its amelioration by N-acetyl cysteine´. *Hum. Exp. Toxicol.*, 39(5): 696-711. DOI: 10.1177/0960327119897759 .

Asim, K., Selman, Y., Suleyman, Y., et al. (2016). ´Heart attack in the course of lithium overdose´. *Iran. Red Crescent Med. J.*, 18(7): e21731. doi: 10.5812/ircmj.21731.

Brozmanová, J., Mániková, D., Vlcková, V. et al. (2010). ´Selenium: A double-edged sword for defense and offence in cancer´. *Arch Toxicol.*, 84 p.p. 919-938. DOI: 10.1007/s00204-010-0595-8.

Chen, K.P., Shen, W.W. and Lu, M.L. (2004). ´Implication of serum concentration monitoring in patients with lithium intoxication´. *Psychiatry Clin. Neuosci*., 58(1) p.p. 25-29. DOI: 10.1111/j.1440-1819.2004.01188.x.

Defo Deeh, P.B., Watcho, P., Wankeu-Nya, M., et al. (2019). ´The methanolic extract of Guibourtia tessmannii (Caesalpiniaceae) and selenium modulate cytosolic calcium accumulation, apoptosis and oxidative stress in R2C tumour Leydig cells: Involvement of TRPV1 channels´. *Andrologia*, 51:e13216. DOI: 10.1111/and.13216.

Diwakar, B.T., Korwar, A.M., Paulson, R.F. et al. (2017). ´The regulation of pathways of inflammation and resolution in immune cells and cancer stem cells by selenium´, *Adv. Cancer Res*., 136 p.p. 153-172. DOI: 10.1016/bs.acr.2017.07.003.

Efrati, S., Averbukh, M., Berman, S., et al. (2005). ´N-acetylcysteine ameliorates lithium-induced renal failure in rats´. *Nephrol. Dial. Transplant.*, 20 p.p. 65–70. DOI: 10.1093/ndt/gfh573.

Feng, J., Schaus, B.J. and Fallavollita, J.A. (2001). ´Preload induces troponin I degradation independently of myocardial ischemia´. *Circulation*, 103 p.p. 2035–2037. DOI: 10.1161/01.cir.103.16.2035.

Hamed, A., Mantawy, E., El-Bakly, W., et al. (2020). ´Putative anti-inflammatory, antioxidant, and anti-apoptotic roles of the natural tissue guardian methyl palmitate against isoproterenol-induced myocardial injury in rats´. *Futur J. Pharm. Sci*., 31 (2020).

https://doi.org/10.1186/s43094-020-00044-y.

Hammadi, M.H., labiy, N.M., Hamoodi, S.R. (2015). ´Study the predictive value of troponin –I and histopathological changes during acute and chronic myocardial infarction in adult male rats´. *Al-Mustansiriyah*

Journal of Science, 26(2) p.p. 13-17. https://www.iasj.net/iasj?aId=110800&func=fulltext.

Henry, C. (2002). ´Lithium side-effects and predictors of hypothyroidism in patients with bipolar disorder: sex differences´. *J. Psychiatry Neurosci*., 27(2) p.p. 104-107.

https://pubmed.ncbi.nlm.nih.gov/11944505/.

Horton, S., Tuerk, A., Cook, D., et al. (2012). ´Maximum recommended dosage of lithium for pregnant women based on a PBPK model for lithium absorption´. *Advances in Bio-informatics*, 2012, 352729.

https://doi.org/10.1155/2012/352729.

Jokinen, M.P., Lieuallen, W.G., Boyle, M.C., et al. (2011). ´Morphologic aspects of rodent cardiotoxicity in a retrospective evaluation of national toxicology program studies´. *Toxicologic Pathology*, 39(5) p.p. 850-860.

DOI: 10.1177/0192623311413788.

Kattoor, A.J., Pothineni, N.V.K., Palagiri, D., et al. (2017). ´Oxidative stress in atherosclerosis´, *Curr. Atheroscler. Rep*., 18; 19(11) p.p. 42. DOI: 10.1007/s11883-017-0678-6

Kim, S. H., Johnson, V. J., Shin, T. Y., et al. (2004). ´Selenium attenuates lipopolysaccharide-induced oxidative stress responses through modulation of p38 MAPK and NF-kappaB signaling pathways´. *Exp. Biol. Med. (Maywood)*, 229(2) p.p. 203-213. DOI: 10.1177/153537020422900209.

Mezni, A., Aoua, H., Khazri, O., et al. (2017). ´Lithium induced oxidative damage and inflammation in the rat's heart: protective effect of grape seed and skin extract´. *Biomed. Pharmacother.*, 95 p.p. 1103–1111.

DOI: 10.1016/j.biopha.2017.09.027.

Nair, A. B., and Jacob, S. (2016). ´A simple practice guide for dose conversion between animals and human´. *J. Basic Clin. Pharm*., 7(2) p.p. 27–31. DOI: 10.4103/0976-0105.177703.

Nciri, R., Allagui, M.S., Bourogaa, E., et al. (2012). ´Lipid peroxidation, antioxidant activities and stress protein (HSP72/73, GRP94) expression in kidney and liver of rats under lithium treatment´. *J. Physiol. Biochem*., 68(1) p.p. 11–18. DOI: 10.1007/s13105-011-0113-3.

Nciri, R., Allagui, M.S., Croute, F., et al. (2008). ´Effects of low doses of Lithium carbonate injected into mice. Functional changes in kidney seem to be related to the oxidative status´. *C. R. Biol*., 331(1) p.p. 23-31. DOI: 10.1016/j.crvi.2007.11.004.

Özsobaci, P.N, Ergün D., Durmus S., et al. (2018). ´Selenium supplementation ameliorates electromagnetic field-induced oxidative stress in the HEK293 cells´. *J. Trace Elem. Med. Biol*., 50 p.p. 572-579. DOI: 10.1016/j.jtemb.2018.04.008.

Park, H. S., Park, E., Kim, M. S., et al. (2000). ´Selenite inhibits the c-Jun N-terminal kinase/ stress -activated protein kinase (JNK/SAPK) through a thiol redox mechanism´. *J. Biol. Chem*., 275(4) p.p. 2527-2531. DOI: 10.1074/jbc.275.4.2527.

Shah, N., Mohd, G., Bhat, G., et al. (2015). ´Lithium carbonate induced histopathological changes in the heart of albino rats´. *World J. Pharm. Pharm. Sci.*, 4 (8) p.p. 1684-1692. DOI:10.9790/3008-09314548.

Shen, J., Li, X., Shi, X., et al. (2020). ´The toxicity of lithium to human cardiomyocytes´. *Environ. Sci. Eur*., 32 p.p. 59. https://doi.org/10.1186/s12302-020-00333-6.

Suchal, K., Malik, S., Gamad, N., et al. (2016). ´Kampeferol protects against oxidative stress and apoptotic damage in experimental model of isoproterenol-induced cardiac toxicity in rats´. *Phytomedicine,* 23 p.p. 1401–1408. DOI: 10.1016/j.phymed.2016.07.015.

Vasbinder, M.A. and Locke, P. (2016). ´Introduction: Global laws, regulations, and standards for animals in research´. *ILAR J.,* 57(3) p.p. 261–265. https://doi.org/10.1093/ilar/ilw039.

Vijaimohan, K., Mallika, J. and Shyamala, C.S.D. (2010). ´Chemoprotective effect of sobatum against lithium-induced oxidative damage in rats´. *J. Young Pharm*., 2(1) p.p. 68–73. DOI: 10.4103/0975-1483.62217.

Yoon, S. O., Kim, M. M., Park, S. J., et al. (2002). ´Selenite suppresses hydrogen peroxide-induced cell apoptosis through inhibition of ASK1/JNK and activation of PI3-K/Akt pathways´. *FASEB J*., 16(1) p.p. 111-113. DOI: 10.1096/fj.01-0398fje.

Yu, R.A., Xia, T., Wang, A.G., et al. (2006). ´Effects of selenium and zinc on renal oxidative stress and apoptosis induced by fluoride in rats´. *Biomed. Environ. Sci*., 19(6) p.p. 439-444. https://pubmed.ncbi.nlm.nih.gov/17319268/

Yüksel, E., Nazyroglu, M., Sahin, M. et al. (2017). ´Involvement of TRPM2 and TRPV1 channels on hyperalgesia, apoptosis and oxidative stress in rat fibromyalgia model: Protective role of selenium´. *Sci. Rep*., 7(1) p.p. 17543. DOI: 10.1038/s41598-017-17715-1.

تقييم التأثير السمي الذي يسببه الليثيوم على القلب في الفئران والتأثير المحتمل للسيلينيوم: دراسة دون المزمنة

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يستخدم دواء الليثيوم في علاج الكثير من الاضطرابات العصبية والنفسية. تعد دراسة التأثيرات السامة لهذا الدواء أمرًا ضروريًا لأن الأطباء كثيرًا ما يصفوا هذا الدواء لمرضاهم في صورة علاج طويل الأمد. هدفت الدراسة الحالية الي دراسة ما إذا كان الليثيوم له تأثير سام على قلوب الجرذان وآليته المحتملة وكذا تأثير السلينيوم. شملت الدراسة أربع مجموعات متساوية من الجرذان (٦ في كل مجموعة) وكانت كلاتي: المجموعة الضابطة، مجموعة السيلينيوم (٠,٢ مجم / كجم / يوم) مذاب في الماء المقطر ويعطي عن طريق الفم ، مجموعة الليثيوم (٥٣ مجم / كجم / يوم) من كربونات الليثيوم عن طريق الفم ، ومجموعة الليثيوم +السيلينيوم كما في الجرعات السابقة. بعد ٩٠ يومًا ، أظهرت الفئران التي تلقت الليثيوم (٥٣ مجم / كجم / يوم) زيادة كبيرة في مستوى مالونديالديهيد (MDA) وانخفاض كبير في مستوى الجلوتاثيون (GSH) مقارنة بالجموعة الضابطة مما يشير إلى التلف التأكسدي في أنسجة القلب. بالإضافة إلى ذلك ، كان هناك ارتفاع ملحوظ في مستوى تروبونين القلب I بالدم (cTnI) . كما أظهر فحص الكيمياء النسيجية المناعية للقلب باستخدام الصبغة المناعية الهستوكيميائية (caspase-3) زيادة كبيرة في مجموعة الليثيوم مقارنة بباقي المجموعات. تشير نتائج الدراسة الحالية إلى أن التاثير الذي يسببه الليثيوم علي قلب الفئران بسبب الإجهاد التأكسدي و موت الخلايا المبرمج. هذا وقد خفف السيلينيوم بشكل كبير من تأثيرات الليثيوم السمية علي القلب لذا يمكن استخدامه لتقليل التأثير السام.