Avrupa Bilim ve Teknoloji Dergisi
Sayı 38, S. 435-439, Ağustos 2022
© Telif hakkı EJOSAT'a aittir
Araştırma Makalesi

www.ejosat.com ISSN:2148-2683

European Journal of Science and Technology
No. 38, pp. 435-439, August 2022
Copyright © 2022 EJOSAT
Research Article

The Effect of Lithium Toxicity on the Goldfish (*Carassius auratus*) Brain

Sama Amer Abbas El-Tekreti[1*], Aslı Çilingir Yeltekin[1]

[1*] Sama Amer Abbas El-Tekreti, University of Van Yuzuncu Yil, Faculty of Science, Departmant of chemistry, van, Turkey, (ORCID: 0000-0003-2480-4567), samasama.90@yahoo.com
[1] Aslı Çilingir Yeltekin University of Van Yuzuncu Yil, Faculty of Scienc, Departmant of chemistry, van, Turkey, (ORCID:0000-0003-0071-7434) aslicyeltekin@gmail.com

(First received 1 July 2022 and in final form 21 August 2022)

(**DOI:** 10.31590/ejosat.1139370)

REFERENCE: El-Tekreti, S., Çilingir Yeltekin, A. (2022). The Effect of Lithium Toxicity on the Goldfish (*Carassius auratus*) Brain. *Avrupa Bilim ve Teknoloji Dergisi*, (38), 435-439.

Abstract

Although lithium is widely used as a standard in decreasing episodes of depression and mania, for its long-term stabilization and efficacy in reducing suicide risk, its use has recently declined due to side effects and the associated toxicity burden. We did this study with the Carassius auratus fish as a model to learn about the adverse effects and toxicity of lithium on the brain. The spectrophotometric approach was used to investigate the effects of a lithium dosage (50 mg/L) in *Carassius auratus* at various periods (24 h, 48 h, 72 h, and 96). As a result, the enzymes Catalase (CAT), Superoxide Dismutase (SOD), and Glutathione Peroxidase (GSH-Px) in the Carassius auratus brain were shown to be altered by lithium chloride (LiCl).

Keywords: Lithium, toxicity, *Carassius auratus*, CAT, SOD, GSH-Px

Lityum Toksisitesinin Japon Balığı (*Carassius auratus*) Beynine Etkisi

Öz

Lityum, depresyon ve mani ataklarını azaltmada yaygın olarak standart olarak kullanılmasına rağmen, uzun vadeli stabilizasyonu ve intihar riskini azaltmadaki etkinliği nedeniyle, kullanımı yan etkiler ve ilişkili toksisite yükü nedeniyle son zamanlarda azalmıştır. Bu çalışmayı, lityumun beyin üzerindeki olumsuz etkileri ve toksisitesini öğrenmek için model olarak Carassius auratus balığı ile yaptık. Lityum dozajının (50 mg/L) Carassius auratus'taki etkilerini çeşitli periyotlarda (24 saat, 48 saat, 72 saat ve 96) araştırmak için spektrofotometrik yaklaşım kullanıldı. Sonuç olarak Carassius auratus beynindeki Katalaz (CAT), Süperoksit Dismutaz (SOD) ve Glutatyon Peroksidaz (GSH-Px) enzimlerinin lityum klorür (LiCl) tarafından değiştirildiği gösterildi.

Anahtar Kelimeler: Lityum, Toksite, *Carassius auratus*, CAT, SOD, GSH-Px

* Corresponding Author: samasama.90@yahoo.com

1. Introduction

Lithium is the member of the alkali metal family. Lithium refers to a group of lithospheric elements in their geochemical characteristics. These elements'ions have enormous size. These elements include potassium, rubidium, and cesium. The top continental crust has 21 g/ton of lithium, while saltwater contains 0.17 mg/l (Pilson, 2012).

Lithium is increasingly used in batteries, alloys, and pharmaceuticals. Lithium is also known as a psychoactive drug, used since the 1950s as a mood stabilizer. It also has an effect on the physiology and organization of the body for some species (Aral & Vecchio-Sadus, 2008). In 2002, the worldwide depletion of pure lithium was projected to be at 5,000 tons (Kszos,2003).

Some research has revealed that dissolution of lithium may occur during ore processing, with tailing water containing 13 mg L/L. (Aral & Vecchio-Sadus, 2008). Li concentrations in major lakes range from 0.014 to 14 mg/L across the world. With its expanding application in several industries, lithium output has expanded dramatically in recent years (from 28 to 43 thousand tons between 2010 and 2017) (Labbé and Daw, 2012).

Lithium (Li) occurs naturally in soil and water, and plant absorption enters the food chain. According to research, lithium levels in blood plasma are roughly proportionate to lithium consumption (De Roos et al., 2001, Richelson,1977).

Because there are many sources of lithium in surface and groundwater from recycling facilities, chemical industraztion, and nuclear-related waste disposal areas, it affects embryonic development in fish (Stachel et al., 1993) and plasma membrane protein modeling in amphibian embryos (Lazou and Beis, 1993). In oceans and coastal areas, factors (temperature, salinity, pH, and trophic environment) can influence the lithium accumulation capabilities of an organism (Ansari et al., 2004; Luoma, 1983).

Li has been demonstrated to impact levels of arachidonic acid (AA), one of the most prevalent fatty acids in the brain, which may explain its activity as a mood stabilizer. Free fatty acids such as AA play a role in active cellular transport (the movement of ions or molecules across the cell membrane) through their effect on compounds that affect osmosis, prompting researchers to study the formation of ions and ion transport proteins that are involved in active transport.

In a municipal wastewater treatment facility in Denmark, lithium concentrations were between 5 and 6 mg/kg. Li toxicity in fish was equivalent to uranium toxicity in zebrafish, which has a LC50 of 88 mg/L (Hamilton, 1995). The possible toxicity of lithium as a result of environmental exposure and therapeutic excess has already been investigated. A research on the toxicity of lithium discovered that Li may have a mechanism similar to copper in that it hampered energy generation and ion control (Aral & Vecchio-Sadus, 2008). Through the chloride cells in the gills of the fish, ion osmosis takes place, where these cells are the controllers of this process. These cells are partially covered by respiratory cells. Li is absorbed via the sodium channel in the gills (Grosell and Wood., 2002. Bury et al., 2003).

2. Material and Method

Carassius auratus were taken from van Lake (Turkey) and transferred to Van Yuzuncu Yil University. Two glass tanks with a capacity of 10.0 L were used and forty-eight fish (1.80 ± 0.05 g) were distributed randomly. Fishes were housed for 5 days and fed regularly twice a day on a commercial diet without lithiu. Tanks containing fish were kept in a period of natural light and continuous ventilation. The water temperature was 25.0 ± 1 °C. Li treatments were performed on Carassius auratus in one tank. The concentration of LiCl was increased, and the final concentration of Lithium in one glass tank was 50 mg/L. (28 fish).The fish were divided into 20 fish into the control group and 28 fish with application group. In the 24, 48, 72 and 96 hours, fish were collected for sampling. When sampling, fish were drugged by MS 222 (0,1 g/L). Tissue was homogenized and stored at −18 °C until analyzed.

2.1. Biochemical Analysis

Using the randox-Ransod assay, superoxide dismutase (SOD) activity was measured at 37 °C, 505 nm and under UV spectrum (Shimadzu UV-1201, UV-Vis Japan) (Xia et al., 1995). Based on the decomposition of hydrogen peroxide (H_2O_2) under 240 nm a UV spectrophotometer approach was used to evaluate CAT enzyme activity (Aebi, 1984). The Placer (1966) technique was used as a pink-violet absorption spectrophotometer under 532 nm, which was detected upon the interaction of thiobarbituric acid TBA and MDA. In order to determine the activity of GSH-Px in plasma, Randox-Ransod enzyme kit was used at 37 °C and 340 nm by the UV spectrum.

2.2. Statistical Analysis

To compare study groups, $p<0.05$ was used to determine statistically significant differences. The data were offered as mean values ± with a standard error of the mean (s.e.m). SPSS was used to do statistical analysis on all data (version 23.0 Inc).

3. Results and Discussion

3.1. Results

Effects of Lithium Chloride Toxicity on SOD and GSH-Px Activity in Carassius auratus Brain

In Figures 1 and 2, the effects of lithium chloride on SOD and GSH-Px activity in the Carassius auratus brain exhibited a considerable increase when compared to the control group. Throughout the study, lithium chloride exhibited a noticeable influence on SOD and GSH-Px activity.

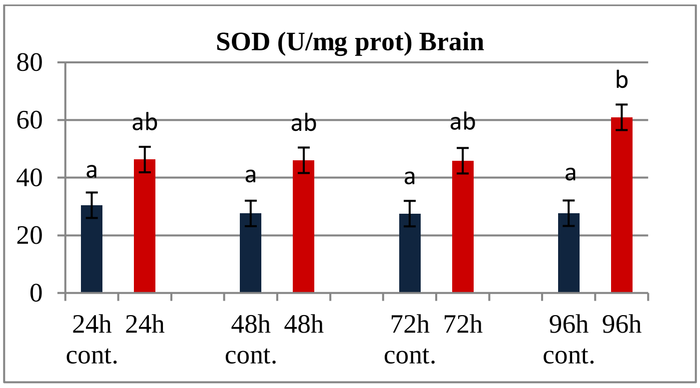

Figure1. Effects of lithium chloride on SOD activity in Carassius auratus brain

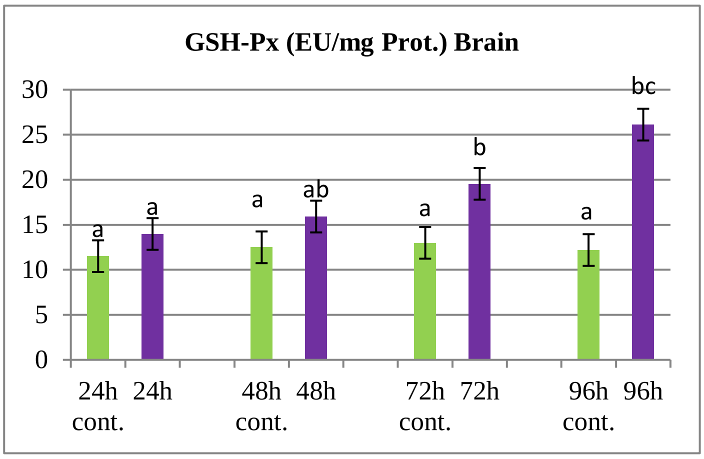

Figure2. Effects of lithium chloride on GSH-Px activity in *Carassius auratus* brain

Effects of Lithium chloride toxicity on CAT and BChE activity in *Carassius auratus* tissue

CAT activity in the brain of Carassius auratus treated with lithium chloride was significantly lower than in the control group ($p < 0.05$)(Figure. 3).In 96h, an increase in the activity of catalase was observed. BChE activity was decreased in the brains of fish exposed to lithium chloride ($P < 0.05$) (Figure 4).

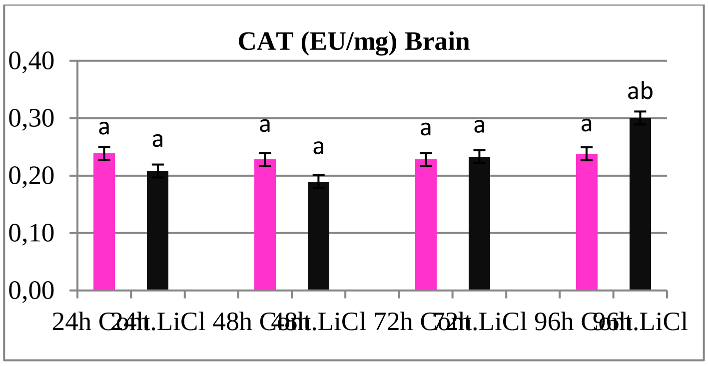

Figure3. Effects of lithium chloride on CAT activity in Carassius auratus brain

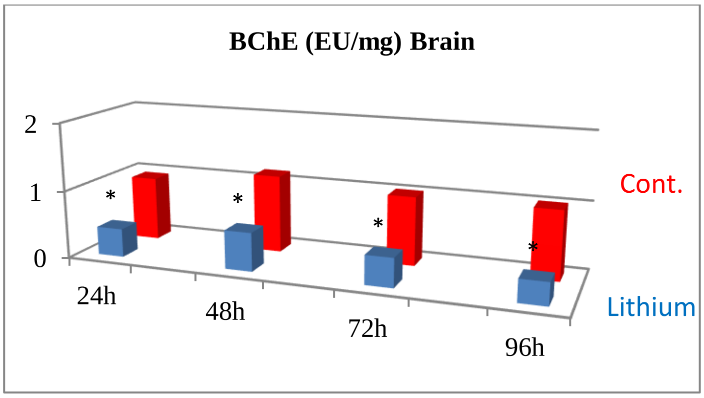

Figure4. Effects of lithium chloride on BChE activity in Carassius auratus brain

4. Discussion

Mineral-induced alterations in the physiology and survival of aquatic creatures under mineral stress are complicated because they differ from mineral to mineral and species to species. The precise causes of mortality from heavy metal poisoning are many and are mostly determined by the metal content in the environment and time.

Fish have only been employed as experimental subjects in a few lithium behavioral experiments, but the results have already supplied some helpful information that may have been included in a general model of lithium action. When fish are given a regular dose of poison, their tolerance drops over time, and the toxin has more time to affect them.

Monitoring changes in enzyme activity in tissues is critical for determining fish physiological state and diagnosing fish illnesses. In this study, it was discovered that lithium chloride altered BChE CAT, SOD, and GSH-Px enzyme activity in Carassius auratus brain tissue.

The goldfish has been found to be an excellent model for biological studies as it readily absorbs water-soluble substances. Its tissues balance over a short period with the solutions in which it swims. Mineral accumulation levels in fish tissues vary according to the species of fish, age patterns, physical and chemical features, and the chemical condition of the environment in which they reside (ThangaMalathi and Anuradhaf, 2020). Environmental pollutants can either boost or decrease the activity of antioxidant enzymes.

In our study reveals an increased level of SOD in brain tissues of Carassius auratus fish treated with lithium chloride indicating a detoxification mechanism against toxicity(Figure1), This rise is owing to the cells' constant generation of O_2^-superoxide anion, as well as their stimulation and reactivation to create the enzyme(Oruç, 2010).

Dimitrova et al. (1994) found a comparable increase in superoxide dismutase activity in Cyprinus carpio after exposure to zinc and lead. Farombi et al. (2008) discovered that SOD activity rises in Butachlor-treated liver and kidneys in Clarias gariepinus. Stara et al. (2012) confirmed the SOD modification by seeing comparable changes in the muscles of the common carp Cyprinus carpio after treatment with Simazine.

In order to counteract the cell damage caused by poisoning in fish, the activity of antioxidant enzymes is either enhanced or decreased. Increased SOD activity in Carassius auratus implies an increased antioxidant state in an effort to counteract the effects of ROS. Anusuya and Hemalatha (2014) also discovered a time-dependent increase in superoxide dismutase activity in Channa striatus treated to 2, 4-D pesticide.

GSH-Px activity was elevated in the brain following lithium chloride exposure (Figure 2), which might be attributed to increased synthesis and enzyme stimulation by H_2O_2 generated from O_2. (Ahmad et al., 2000). GSH-Px activation was shown to be increased in Carpio and Ictalurus nebulosus exposed to dichlorvos (Varga and Matkovics,1997).

CAT is an active enzyme that is the first to exhibit changes once oxidative stress is induced (Jin et al., 2010). In our study, we observed a decreased in the CAT level in *Carassius auratus* brain at 24 hours due to oxidative stress caused by lithium chloride toxicity (Figure 3). Then the CAT level was increased in the brain after exposure to lithium chloride for 96 hours, the increases in these enzyme activity is likely in response to toxic stress and neutralize the effect of increased generation of reactive oxygen species (John et al., 2001). In the 7-day exposure group, groups treated with CBZ had higher CAT activity than the control group (Li, Zhi-Hua et al.,2010).

One of the neurotransmitter systems implicated in the pathophysiology of mood disorders is the cholinergic system. (Furey and Drevets, 2006). Cholinesterase biomarkers have been widely used in a variety of species. When organisms are exposed to harmful compounds, such as polycyclic aromatic hydrocarbons, organophosphates, and carbamates, these enzymes are activated. Cholinesterase inhibition has been examined in many organs and systems Specifically in brain tissue (Boer et al., 1993). Fish with higher enzyme activity, according to Murphy et al, exhibit increased enzyme inhibition following pesticide exposure. Our findings corroborate these conclusions. Because of their great sensitivity and presentation of the earliest identifiable evidence of sublethal stress response in organisms, biomarkers are effective indicators of pollution (Braunbeck et al.,1995). Because enzyme activity in target tissues contributes to neurotransmission, blocking cholinesterase in the nervous system or muscle harms organisms (Padilla, 1995).

According to research, lithium may interact with the cholinergic system selectively (Bhalla et al., 2007). Lithium has been demonstrated to increase seizures in the central nervous system caused by pilocarpine, physostigmine, neostigmine, and other cholinergic mimetics, which can be avoided by either anticholinergic or anticonvulsant medications (Chaudhary and Gupta, 2001).

Our study notice a significant inhibiting in BChE (Butyrylcholinesterase) activity in the brains of *Carassius auratus* fish when treated with lithium chloride compared to the control groups (Figure 4). As is known, the primary role of BChE regulating brain acetylcholine (ACh) levels (O'Brien,2016, Silver,1974). As a result, if the concentration of ACh is high, BChE will be more successful in compartmentalizing it. In this regard, it is worth noting that in our investigation, BChE activity levels in *Carassius auratus* were connected to AChE activity levels in the brain.

5. Conclusions

The results obtained showed that lithium compounds have a positive effect on the toxic metabolism in the fish brain by inhibiting the antioxidant activities.

The researchers discovered alterations in oxidative stress indicators and antioxidant defenses in the brain of Carassius auratus following long-term exposure to lithium chloride. According to the current findings, when Carassius auratus tissue is exposed to lithium chloride, antioxidant activity (SOD, GSH-Px, and CAT) and antioxidant gene expression are boosted in an attempt to counteract the effect of reactive oxygen species.

It is necessary to study the possible relationship between oxidative stress and the chemo physiological response of different aquatic organisms using the long exposure time in other studies. In terms of lithium applications, the biochemical processes associated with the functional expression of target genes and antioxidant defense in this work may make major contributions to the literature. Based on these findings, we feel that research into the harmful effects of lithium compounds and the enhancement of the antioxidant defense system should be broadened.

In the setting of BuChE inhibition in brain tissues, LiCl is very hazardous. At different amounts of exposure, LiCl had varying effects on brain functioning, including neurotransmission. Because of the very poisonous lithium chloride, they must be thoroughly monitored in the environment in order to limit the deleterious effects on creatures.

ACKNOWLEDGMENT This study was supported by the project of Van Yuzuncu Yil University, Scientific Research Projects with FBA-2021-9332 project.

References

Aebi, H. (1984). [13] Catalase in vitro. In Methods in enzymology (Vol. 105, pp. 121-126). Academic press.

Ahmad, I., Hamid, T., Fatima, M., Chand, H. S., Jain, S. K., Athar, M., & Raisuddin, S. (2000). Induction of hepatic antioxidants in freshwater catfish (Channa punctatus Bloch) is a biomarker of paper mill effluent exposure. Biochimica et Biophysica Acta (BBA)-General Subjects, 1523(1), 37-48.

Ansari, T. M., Marr, I. L., & Tariq, N. (2004). Heavy metals in marine pollution perspective-a mini review. Journal of Applied Sciences, 4(1), 1-20.

Anusuya, L., & Hemalatha, O. (2014). Effect of 2, 4-D pesticide on fish physiology and its antioxidant stress. World Journal of Fish and marine Sciences, 6(1), 98-100.

Aral, H., & Vecchio-Sadus, A. (2008). Toxicity of lithium to humans and the environment—a literature review. Ecotoxicology and environmental safety, 70(3), 349-356.

Bhalla, P., Garg, M. L., & Dhawan, D. K. (2010). Protective role of lithium during aluminium-induced neurotoxicity. Neurochemistry international, 56(2), 256-262.

Braunbeck, T., Hauck, C. R., Scholz, S., & Segner, H. (1995). Mixed function oxygenases in cultured fish cells: contributions of in vitro studies to the understanding of MFO induction. Zeitschrift für angewandte Zoologie, 81, 55-72.

Bury, N. R., Walker, P. A., & Glover, C. N. (2003). Nutritive metal uptake in teleost fish. Journal of experimental biology, 206(1), 11-23.

Chaudhary, G., & Gupta, Y. K. (2001). Lithium does not synergize the peripheral action of cholinomimetics as seen in the central nervous system. Life Sciences, 68(18), 2115-2121.

De Boer, J. D., Stronck, C. J. N., Traag, W. A., & Van der Meer, J. (1993). Non-ortho and mono-ortho substituted chlorobiphenyls and chlorinated dibenzo-p-dioxins and dibenzofurans in marine and freshwater fish and shellfish from the Netherlands. Chemosphere, 26(10), 1823-1842.

De Roos, N. M., de Vries, J. H., & Katan, M. B. (2001). Serum lithium as a compliance marker for food and supplement intake. The American journal of clinical nutrition, 73(1), 75-79.

Dimitrova, M. S., Tishinova, V., & Velcheva, V. (1994). Combined effect of zinc and lead on the hepatic superoxide dismutase-catalase system in carp (Cyprinus carpio). Comparative Biochemistry and Physiology Part C: Pharmacology, Toxicology and Endocrinology, 108(1), 43-46.

Farombi, E. O., Ajimoko, Y. R., & Adelowo, O. A. (2008). Effect of butachlor on antioxidant enzyme status and lipid peroxidation in fresh water African catfish,(Clarias gariepinus). International journal of environmental research and public health, 5(5), 423-427.

Furey, M. L., & Drevets, W. C. (2006). Antidepressant efficacy of the antimuscarinic drug scopolamine: a randomized, placebo-controlled clinical trial. Archives of general psychiatry, 63(10), 1121-1129.

Grosell, M., & Wood, C. M. (2002). Copper uptake across rainbow trout gills: mechanisms of apical entry. Journal of Experimental Biology, 205(8), 1179-1188.

Hamilton, H. (1995). The thermal cycling behaviour of lithium titanate. Journal of nuclear materials, 219, 274-283.

Jin, Y., Zhang, X., Shu, L., Chen, L., Sun, L., Qian, H., ... & Fu, Z. (2010). Oxidative stress response and gene expression with atrazine exposure in adult female zebrafish (Danio rerio). Chemosphere, 78(7), 846-852.

John, S., Kale, M., Rathore, N., & Bhatnagar, D. (2001). Protective effect of vitamin E in dimethoate and malathion induced oxidative stress in rat erythrocytes. The Journal of nutritional biochemistry, 12(9), 500-504.

Kszos, L. A., & Stewart, A. J. (2003). Review of lithium in the aquatic environment: distribution in the United States, toxicity and case example of groundwater contamination. Ecotoxicology, 12(5), 439-447.

Labbé, J. F., & Daw, G. (2012). Panorama 2011 du marché du lithium (Doctoral dissertation, Bureau de recherches géologiques et minières [BRGM]; Centre d'Economie de la Sorbonne [CES]).

Lazou, A., & Beis, A. (1993). Lithium induces changes in the plasma membrane protein pattern of early amphibian embryos. Biology of the Cell, 77, 265-268.

Li, Z. H., Velisek, J., Zlabek, V., Grabic, R., Machova, J., Kolarova, J., & Randak, T. (2010). Hepatic antioxidant status and hematological parameters in rainbow trout, Oncorhynchus mykiss, after chronic exposure to carbamazepine. Chemico-biological interactions, 183(1), 98-104.

Luoma, S. N. (1983). Bioavailability of trace metals to aquatic organisms—a review. Science of the total environment, 28(1-3), 1-22.

Murphy, H. M., & Jenkins, G. P. (2010). Observational methods used in marine spatial monitoring of fishes and associated habitats: a review. Marine and Freshwater Research, 61(2), 236-252.

O'Brien, R. D. (2016). Toxic phosphorus esters: Chemistry, metabolism, and biological effects. Elsevier.

Oruç, E. Ö. (2010). Oxidative stress, steroid hormone concentrations and acetylcholinesterase activity in Oreochromis niloticus exposed to chlorpyrifos. Pesticide biochemistry and physiology, 96(3), 160-166.

Padilla, S. (1995). Regulatory and research issues related to cholinesterase inhibition. Toxicology, 102(1-2), 215-220.

Pilson, M. E. (2012). An Introduction to the Chemistry of the Sea. cambridge university press.

Placer, Z. A., Cushman, L. L., & Johnson, B. C. (1966). Estimation of product of lipid peroxidation (malonyl dialdehyde) in biochemical systems. Analytical biochemistry, 16(2), 359-364.

Richelson, E. (1977). Lithium ion entry through the sodium channel of cultured mouse neuroblastoma cells: a biochemical study. Science, 196(4293), 1001-1002.

Silver, A. (1974). The biology of cholinesterases.

Stachel, S. E., Grunwald, D. J., & Myers, P. Z. (1993). Lithium perturbation and goosecoid expression identify a dorsal specification pathway in the pregastrula zebrafish. Development, 117(4), 1261-1274.

Stara, A., Machova, J., & Velisek, J. (2012). Effect of chronic exposure to simazine on oxidative stress and antioxidant response in common carp (Cyprinus carpio L.). Environmental Toxicology and Pharmacology, 33(2), 334-343.

ThangaMalathi, S., & Anuradha, V. (2020). Lithium Induced Toxicity Profile of Oxygen Consumption, Haematological Parameters and Biochemical Profiles of Channa punctatus and Oreochromis niloticus. Nature Environment & Pollution Technology, 19(2).

Varga, S. I., & Matkovics, B. (1997). Organophosphate effects on antioxidant system of carp (Cyprinus carpio) and catfish (Ictalurus nebulosus). Comparative Biochemistry and Physiology Part C: Pharmacology, Toxicology and Endocrinology, 117(1), 83-88.

Xia, Z., Dickens, M., Raingeaud, J., Davis, R. J., & Greenberg, M. E. (1995). Opposing effects of ERK and JNK-p38 MAP kinases on apoptosis. Science, 270(5240), 1326-1331.