2025, Scienceline Publication
World's Veterinary Journal
World Vet J, 15(2): 534-542.
ISSN 2322-4568

DOI: https://dx.doi.org/10.54203/scil.2025.wvj53
PII: S232245682500053-15

Pharmacological Roles of Lithium in Treatment of Diseases: New Insights

Marwa Elsayed Ghamry[1]*, Islam Ahmed Ibrahim[2], Shimaa Mustafa Elshazly[2], and Ahmed Fahmy[2]

[1]*Al-Ahrar Teaching Hospital, Zagazig, Sharkia, Egypt*
[2]*Department of Pharmacology and Toxicology, Faculty of Pharmacy, Zagazig University, Egypt*

*Corresponding author's Email: marwa_pharm11@yahoo.com

REVIEW ARTICLE
Received: April 03, 2025
Revised: May 09, 2025
Accepted: June 01, 2025
Published: June 30, 2025

ABSTRACT

Lithium is a delicate, silvery-white alkali metal, the smallest monovalent cation with the symbol Li and atomic number 3. The present study aimed to discuss the current knowledge of Lithium's pharmacological and toxicological effects, as well as future perspectives on its application in treating various diseases in laboratory animals. Lithium is currently being investigated for its potential role in maintaining beta-cell activity and reducing insulin resistance in mammals, as it exhibits a diverse array of biological effects. The basis of bipolar disorder medication for acute mood periods, switch prevention, preventative treatment, and suicide prevention has been and still is lithium. Lithium has lately been investigated in several neurodegenerative diseases and other psychoses. It has demonstrated potential benefits in experimental animals in avoiding neurodegeneration and brain damage. Neurological conditions, such as traumatic brain damage, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, mercury poisoning, alcoholism, and drug dependence, may benefit from lithium's neuroprotective, antioxidant, and anti-inflammatory qualities. Lithium supports neuronal survival, repairs damage, reduces inflammation and cell death, promotes neurogenesis, maintains cell membranes, and affects signaling pathways related to brain health and recovery. In conclusion, lithium remains a key treatment for bipolar disease due to its mood-stabilizing effects and capacity to lower the risk of relapse and suicide. However, accumulating data suggested that lithium may affect glucose metabolism, potentially causing insulin resistance or decreased glucose tolerance in some people. Additionally, Lithium in rats has anti-inflammatory properties with markedly reduced insulin resistance. These findings emphasize the importance of monitoring metabolic health during long-term lithium treatment to ensure optimal psychiatric and physical health.

Keywords: Glycogen synthase kinase-3, Hyperglycemia, Inflammation, Lithium, Neuroprotection, Oxidative stress

INTRODUCTION

Johan August Arfwedson, a Swedish chemist, discovered lithium (Li) in the mineral petalite in 1817. Brine deposits and mineral springs can also include Li as salt; saltwater has 0.1 parts per million (ppm) of lithium (Balaram, 2024). Additionally, lithium may be found in pegmatite ores, which include spodumene (LiAlSi2O6) and lepidolite of different structures, or amblygonite (LiAlFPO4) ores, which have Li_2O values ranging from 4 to 8.5 %. Lithium comprises around 0.002% of the Earth's crust (Baran, 2019).

Lithium is a well-known inhibitor of glycogen synthase kinase-3 (GSK-3; Smith et al., 2002). The GSK3, as a Serine/threonine kinase, is essential for several biological processes, including cell division, motility, and survival (Eldar-Finkelman, 2002). Through crosstalk with the glucocorticoid (GC) signaling system, it has been shown that pharmacological or genetic inactivation of GSK3 resulted in the abrogation of the detrimental effects of GCs in the β-cell line INS-1 832/13 (Delangre et al., 2021). In the rat brain, the *in vivo* obtained evidence through real-time PCR for Li inhibition of GSK-3 revealed a significant decrease in lithium β-catenin mRNA levels, which may represent compensation for an increase in β-catenin stability (Sinha et al., 2005). Using lithium significantly inhibits brain GSK3 *in vivo* at relevant concentrations to the treatment of bipolar disorder (Gould et al., 2004). Notably, it has been demonstrated that lithium chloride (LiCl) mitigates β-cell mortality and dysfunction caused by GCs in isolated islets of the pancreas (Delangre et al., 2021). For several years, lithium has been utilized to treat bipolar illnesses (Alda, 2015). Such as other medications, lithium usage causes several challenges, including a narrow therapeutic index of lithium, which requires careful monitoring of patients' plasma concentrations (Albayrak et al., 2013). Additionally, lithium treatment leads to side effects, such as decreased renal function (Schoretsanitis et al., 2022) and hypothyroidism (Lazarus, 2009). Long-term effects of Li on rat pups reared on Li chow for three weeks led to regular increased measures of anxiety-like behavior. Gene microarray studies of the amygdala revealed that Li affected the expression of gene transcripts of the synapse and the cytoskeleton, suggesting that the treatment induced synaptic adjustments (Youngs et al., 2006). Nonetheless, more than 60 years of Li administration have demonstrated that side effects are largely controllable with careful patient management (Gitlin, 2016). It is worth noting that Li medication has demonstrated

To cite this paper: Ghamry ME, Ibrahim IA, Elshazly SM, and Fahmy A (2025). Pharmacological Roles of Lithium in Treatment of Diseases: New Insights. *World Vet. J.*, 15(2): 534-542. DOI: https://dx.doi.org/10.54203/scil.2025.wvj53

therapeutic potential in people for conditions other than mental illnesses. For instance, Li has been shown to have immunomodulatory and antiviral properties against the herpes viruses in humans (Rybakowski, 2022). It has also been suggested that Li appears to be multifactorial and is intercorrelated with the functions of several enzymes as GSK3 and inositol monophosphatase (Brown and Tracy, 2013). In addition, Li leads to thyroid hormone system disruption (Chevalier et al., 2024) and vitamins, as well as growth and transforming factors (Schrauzer, 2002). Lithium may potentially be used to treat Alzheimer's disease, according to some clinical investigations (Damiano et al., 2023). Curiously, a plethora of experimental data indicated that administering Li to preclinical models of diabetes in rats enhanced insulin sensitivity and global glucose metabolism (Dangana et al., 2019; Arciniegas et al., 2022). In a rat model of type 2 diabetes, a recent study indicated that Li medication significantly improved glucose metabolism by substantially reducing insulin resistance and reducing the inflammation associated with diabetes (Pitasi et al., 2022). Furthermore, while taking corticosterone for an extended period, LiCl works as an adjuvant therapy to lessen GC-induced insulin resistance and excessive gluconeogenesis (Delangre et al., 2023). Lithium appears to have multiple biochemical modes of action, including impacts on the functioning of different enzymes, hormones, and vitamins and growth and transformation factors (Marshall, 2015; Rizk et al., 2021). Lithium medication may lead to gastrointestinal, immunological, metabolic, nephrogenic, neurologic, sexual, and teratogenic effects (Mehrafza et al., 2017; Jafari et al., 2018). In addition to the Long-term use of Li can affect kidney and thyroid functions (Lieber et al., 2020; Boivin et al., 2023). The present review article focused on the current findings about Li's pharmacological and toxicological effects, and the future perspective of its use in the treatment of different diseases.

TYPE 2 DIABETES

Lithium is primarily known for its use in treating mood disorders, particularly bipolar disorder. However, some studies are exploring lithium effects on diabetes; meanwhile, the use of Li for diabetes management is not shared or standard practice (Rybakowski, 2020). The involvement of Li in the regulation and management of insulin resistance and type 2 diabetes may be ascribed to the inhibition of GSK-3. The GSK-3 is an essential serine/threonine kinase that regulates gene transcription, glycogen formation, protein synthesis, and cell differentiation in a range of cell types. In a previous study, GSK-3 has been connected to the intricate etiology of skeletal muscle insulin resistance in type 2 diabetes in people and obese *Rattus norvegicus* models (Henriksen and Dokken, 2006). Information on the function of GSK-3 as a regulator of insulin action on the muscle glucose transport activity of humans has been obtained from studies involving sensitive and selective GSK-3 inhibitors. These studies have demonstrated that specific GSK-3 inhibition raises insulin-stimulated glucose transport activity in insulin-resistant skeletal muscle in humans (Mathur et al., 2017; Burillo et al., 2021).

Another necessary consequence of GSK-3 inhibitors in type 2 diabetes associated with obesity is decreased hepatic glucose production, most likely due to the downregulation of genes related to gluconeogenesis (Henriksen et al., 2007). Lithium supplementation *in vitro* boosted skeletal muscle glucose uptake, which seemed to be related to higher levels of the glucose transporter type 4 (GLUT4) on the cell surface and lower levels of GLUT4 internalization (Jung et al., 2017). According to specific research, Li shields the insulin-producing islets from oxidative damage caused by apoptosis (cell death), maintains the integrity of the pancreatic islets, and protects the β-cells, which may preserve or enhance insulin secretion in diabetic Wistar rats (Ostrovskaya et al., 2018; Zhang et al., 2021). Lithium has anti-inflammatory properties that may help manage the chronic inflammation linked to diabetes, especially type 2 diabetes, including reducing the expression of cyclooxygenase-2, inhibiting the production of interleukin (IL1)-1 β and tumor necrosis factor-α (TNF-α), and increasing the synthesis of IL-2 and IL-10 (Nassar and Azab, 2014; Hamstra et al., 2023). Although it is not a direct mechanism of glucose control, lithium can have a modest osmotic diuretic action that may aid in lowering hyperglycemia by encouraging the excretion of glucose through urine in rats (Dousa et al., 1976) and in humans (Chambers et al., 1977).

NEUROPROTECTIVE MEDICINE

Bipolar disorder is the primary condition for which lithium is used. However, new studies have indicated that lithium may also treat brain damage due to its neuroprotective and neuroplasticity properties (Machado-Vieira et al., 2006; Alda, 2015; Rana and Singh, 2018). Here is an overview of lithium's potential role in treating brain injuries in rats. Lithium has been identified as an effective neuroprotective agent that prevents apoptosis-related cell death in rats. Lithium neuroprotection in rats is achieved through multiple intersecting mechanisms, although the specific mechanisms by which lithium interacts with these mechanisms remain under investigation (Khan et al., 2016). Through inducing brain-derived neurotrophic factors, Li maximizes cell survival, stimulating activities in anti-apoptotic pathways, including the

phosphatidylinositol 3-kinase/Akt and the mitogen-activated protein kinase pathways (Rana and Singh, 2018). In cultured rat cell lines, lithium reduces the pro-apoptotic function by directly and indirectly inhibiting GSK-3β activity as well as indirectly inhibiting calcium influx caused by N-methyl-D-aspartate (NMDA) receptor activation (Chiu and Chuang, 2011). Lithium-induced regulation of anti- and pro-apoptotic pathways alters a wide variety of downstream effectors, including β-catenin, heat shock factor 1, activator protein 1, cyclic adenosine monophosphate (cAMP) response-element-binding protein, and the B-cell lymphoma-2 (Bcl-2; Rowe and Chuang, 2004; Ghanaatfar et al., 2023). In mouse models of cerebral ischemia, lithium treatment reduces the catalytic activity of certain substrates, leading to the stabilization of β-catenin and nuclear factor erythroid 2 (Nrf2) in the cytosol. This stabilization promotes their translocation to the nucleus, which may enhance the cellular protective response to ischemic injury, as both proteins are crucial regulators of various protective pathways (Chuang et al., 2011).

The β-catenin modulates Tcf/Lef-1-dependent genes implicated in survival, differentiation, and neuron cell cycle dynamics (Nygren et al., 2007). In lithium therapy, pro-inflammatory cytokines such as TNF-α, interleukin (IL)-6, and IL-1β, as well as many other cytotoxic chemicals, including reactive oxygen species (ROS) and prostanoids, were decreased (Rana and Singh, 2018; Medić et al., 2020). By inhibiting the production of key inflammatory cytokines, including IL-1β and TNF-α, Li has demonstrated anti-inflammatory properties. These mechanisms support the efficacy of lithium against neurodegeneration during neuroinflammatory events (Yu et al., 2012; Khan et al., 2017; Mehrafza et al., 2019). Additionally, Li improves synaptic plasticity in humans, which is important for memory and learning. Specific sites and receptors that control the production, release, turnover, and reuptake of neurotransmitters, including serotonin and dopamine, may be impacted by lithium (Puglisi-Allegra et al., 2021). In addition, Li can bind to various synaptic serotonin receptors and increase serotonin release in sixty-nine patients with depression (Baumann et al., 1996). Therefore, the therapeutic effects of lithium may be partly linked to its capability to regulate neurotransmitter signaling within the central nervous system (Contestabile et al., 2013; Dell'Osso et al., 2016). Moreover, lithium influences the Wnt/β-catenin signaling pathway, crucially plays a role in the proliferation of neural precursor cells during the development of the central nervous system (CNS). The Wnt/β-catenin promotes the proliferation of progenitor cells in the developing neural tube, including in the midbrain and hippocampus of mammals (Vallée and Vallée, 2021).

PREVENTING LIVER DAMAGE

Lithium may mitigate liver damage by decreasing inflammatory mediators, such as TNF-α, IL-1, IL-6, interferon (IFN-γ), IL-8, and ROS. Furthermore, inhibition of GSK-3β can enhance longevity in mice suffering from polymicrobial sepsis by improving inflammation through the regulation of nuclear factor (NF-κB) and cAMP responsive element binding protein (CREB). This process helps reduce hepatic apoptosis and liver damage in mice (Zheng et al., 2017). The inhibition of GSK3β ameliorates liver Ischemia/Reperfusion (I/R) injury by decreasing stress-induced cell death, reducing apoptosis, and enhancing liver proliferation in rats (Liu et al., 2013).

SIDE EFFECTS

Lithium has a half-life of 20 to 24 hours in the body. The half-life is prolonged in patients with poor renal function, typically 36 hours and ranging from 40 to 50 hours, as documented (Jafari et al., 2018; Zanandrea et al., 2018). Lithium is often administered as lithium carbonate, which is available in tablet form (0.4 to 2.0 g/day). A concentration between 0.5 and 1.2 mM was considered a beneficial medical spectrum. Toxic effects can occur at doses exceeding 1.5 mM, and life-threatening outcomes may arise at doses of over 3.5 mM (Zanandrea et al., 2018). Nausea, vomiting, loss of appetite, and diarrhea are all common acute adverse impacts of lithium in humans (Lowe et al., 2023). In mice, lithium medication has been associated with negative effects on cognition, dermatology, endocrine, in addition to gastrointestinal, immunological responses, metabolism, kidney function, neurological health, sexual function, and teratogenic outcomes (Jafari et al., 2018). Lithium treatment has been associated with weight gain and sexual dysfunction (Mehrafza et al., 2017). Most of lithium's adverse effects are due to the ability to suppress the enzyme prostatic acid phosphatase (PAP), leading to perturbation of different cellular functions, including RNA processing (Oruch et al., 2014).

Typically, fine hand tremors that are symmetrical are a key characteristic of tremors induced by lithium. The tremors often manifest as postural tremors, in contrast to those caused by antipsychotics in long-term lithium-treated patients (Singh et al., 2023).

The Long-term use of lithium can affect kidney function, potentially leading to chronic kidney disease in individuals receiving treatment (Boivin et al., 2023). Lithium can also affect thyroid function, possibly causing hypothyroidism or goiter (Lieber et al., 2020). The clinical trials indicated that lithium is used in both experimental animals and human cell lines, as detailed in Table 1.

Table 1. Clinical and therapeutic uses of lithium in experimental animals and human cell lines

Species	Dose	Expected uses	Reference
Mice	LiCl (40 or 80 mg/kg bw single intraperitoneal injection).	Low-dose lithium medication promoted renal tubular epithelial regrowth, accelerated kidney restoration, and expedited renal recovery after cisplatin-induced acute kidney injury (AKI). Lithium's protective impact was assumed to be due to the reduction of GSK-3β, which contributed to the preservation of proliferative components, including cyclin D1, c-Myc, and HIF-1a.	Bao et al. (2014)
Rats	LiCl (1 mmol/kg bw/day) for four weeks.	Lithium guarded against ventricular arrhythmias by reducing nerve growth factor-induced sympathetic innervation via antioxidant modulation of the Nrf2/HO-1 circuit.	Lee et al. (2014)
Human colon cancer cell line	LiCl (10, 20, 40, and 60 mM) for six, 12, 24, and 48 hours.	It was revealed that lithium, as a GSK-3β inhibitor, inhibited cell survival and proliferation by inhibiting the ROS/ GSK-3β /NF-κB pathway.	Li et al. (2014)
Rats	LiCl (85 mg/kg bw) for six weeks.	Lithium, as a GSK-3β inhibitor, promoted motor neuron propagation from the CNS to the PNS.	Su et al. (2014)
Human	LiCl (1, 5 mM) for six days.	Lithium boosted MSC proliferation by suppressing GSK-3β activity, β-catenin aggregation, and Wnt pathway activation.	Zhu et al. (2014)
Zebra fish embryo	LiCl (100 µM) for five days.	Amyloid-β injection into zebrafish embryos led to cognitive deficits and elevated tau phosphorylation; both cognitive deficits and elevated tau phosphorylation were reversed by lithium incubation for a 5days.	Nery et al. (2014)
Rat	LiCl (7 µL/g) for 5 weeks	In a glaucoma rat model, LiCl lowered intraocular pressure (IOP) through the phosphorylation of PERK and the control of PERK/ROCK signaling.	Sun et al. (2014)
Rats	LiCl (0.1 mM) for four days.	Lithium stimulated GFP-MSC proliferation and neural differentiation. Furthermore, lithium stimulated the differentiation of transplanted GFP-MSC into more oligodendrocytes, astrocytes, and neurons, enhancing neural regeneration in the rat spinal cord. It represents a viable method for developing a highly effective therapy using mesenchymal stem cells (MSCs) for CNS illnesses.	Dong et al. (2015)
Rats	Li_2CO_3 (2.7 mg /kg bw) for three weeks.	In rats, lithium combined with sodium selenite leads to depletion of plasma CAT (catalase) and slight enhancement of AA (ascorbic acid), as well as a slight increase in MDA (malondialdehyde)	Musik et al. (2015)
Rats	LiCl (0.3-30 mM) for 24 hours.	The PI3K/Akt/FoxO1 pathway was involved in Li's protection against serum-starved cell death.	Zeng et al. (2016)
Monkey	LiCl (0.15, 0.25, 0.75 mEq/kg) before and during induction of anesthesia.	The Li co-administration prevented acute isoflurane-induced neuroapoptosis and reduced oligodendroglia-induced apoptosis.	Noguchi et al. (2016)
Human	LiCl (10, 15, 25 mM) for 72 hours.	The LiCl promoted inhibitory GSK-3β serine 9 phosphorylation in RD and RH-30 cell lines; however, the combined arsenic trioxide (ATO) and LiCl greatly diminished GLI1 protein expression, demonstrating elevated incidences of cell apoptosis. As a result, the combined application of arsenic trioxide and lithium chloride enhances the efficacy of rhabdomyosarcoma therapy.	Schleicher et al. (2017)
Human	LiCl (2 mM) for 24 hours.	The activation of Orai1/STIM1/2 expression and activity in Chorea-Acanthocytosis (ChAc) neurons by lithium was impaired by pharmacological nuclear factor B NFB inhibition.	Sukkar et al. (2018)
Zebrafish	LiCl (100 mg/L) for seven days.	In zebrafish, Li reduced scopolamine-induced memory impairment, decreased exploration, and boosted acetylcholinesterase activity.	Zanandrea et al. (2018)
Mice	LiCl (4, 10, 20, 30, 60 mg/kg bw) for seven days.	By modulating the NMDAR/NO and ERK pathways, Li, as a GSK3 inhibitor, protects rat cerebellar granule neurons from glutamate-induced neurotoxicity.	Jafari et al. (2018)

Rats	LiCl (75, 150, and 300 mg/kg bw) for 28 days.	Lithium protected the hippocampus from methamphetamine-stimulated neurodegeneration via the Akt-1/GSK-3β and CREB/BDNF signaling pathways.	Mehrafza et al. (2019)
Rats	Li_2CO_3 (2.4 g/Kg) for 10 weeks.	In ovariectomized rats, Li medication averted neurobehavioral deficits and increased structural synaptic plasticity. Lithium therapy also masked neuroinflammatory processes due to the reduction of reactive gliosis and the maintenance of blood–brain barrier strength. The Gsk-3β activity and BDNF levels were controlled by Li, which assisted in resisting neuroinflammation, and structural synaptic plasticity was conserved.	Rana et al. (2022)
Mice	LiCl (1 mmol/kg) for 28 days.	Lithium decreased the infarct size, improved the motor execution, and alleviated related affective and cognitive impairments in the framework of ischemia-reperfusion in the middle cerebral artery blockage stroke model in mice.	Chen et al. (2022)
Dogs	LiCl (85 mg/kg) for 28 days in rats. LiCl (5 nM) for three hours in PC12 cells.	When compared to untreated dogs, one male dog being unilaterally cryptorchid (right side), lithium-treated animals had dramatically better trabecular spacing, number, and connection density, and serum bone-specific alkaline phosphatase levels. In comparison to untreated Mucopolysaccharidosis (MPS) I and heterozygous animals, growth plates from lithium-treated animals had more hypertrophic chondrocytes.	Lau et al. (2022)
Rats	LiCl (5 nM) for 3 hours in PC12 cells.	Lithium promoted healing after spinal cord injury by acting as an anti-inflammatory, antioxidant, and anti-pyroptotic agent via the Nrf2/heme oxygenase-1 pathway.	Zhao et al. (2022)
Human	LiCl (10 mM) for 24 hours.	The body's tryptophan catabolism was inhibited by Li. In human-derived microglia, the kynurenine pathway was initiated by boosting inhibitory GSK3S9 phosphorylation and diminishing $STAT1^{S727}$ and $STAT3^{Y705}$ phosphorylation values.	Göttert et al. (2022)
Rats	--	In rats chronically treated with corticosterone, Li treatment markedly reduced insulin resistance.	Delangre et al. (2023)
Rats	1.4 g/kg, 1.8 g/kg, 2.2 g/kg lithium bicarbonate	Lithium adversely influenced the cellular defense system. Furthermore, apart from anti-inflammatory properties, Li exhibited cytokine-mediated inflammatory activities in rat groups.	Matur et al. (2024)
Rats	Four rat groups fed on Li g/kg/diet, and high Li (2.2 g/kg/diet) groups were fed with lithium bicar	The study found that high Li treatment in animals increased malondialdehyde levels, decreased superoxide dismutase and catalase levels, and increased anxiety-like behaviors. The prolonged Li treatment, particularly at doses approaching the higher therapeutic range (2.2 g/kg/diet) for 30 days, induces adverse effects.	Eraslan et al. (2024)

LiCl: Lithium chloride, AKI: Acute kidney injury, BW: Body weight, cyclin D1: Cell cycle regulators, c-Myc encodes a transcription factor, HIF-1 α: Hypoxia-inducible factor 1α, Nrf2/HO-1: Nuclear factor-2/hemeoxygenase-1, ROS/GSK-3β /NF-κB: Reactive oxygen species/glycogen synthase kinase 3β/ nuclear factor-kappa-beta, CNS: Central nervous system, PNS: Peripheral nerve system, MSC: Mesenchymal stem cell, PERK/ROCK: Protein endoplasmic reticulum kinase/Rho-associated protein kinase, GFP: Green fluorescent protein, MSCs: Mesenchymal stem cells, PI3K/Akt/FoxO1: Phosphatidylinositol 3-kinase/ Protein kinase B/ Forkhead boxO1, RD: ERMS cell line, RH-30: ARMS cell line, NFB: Nuclear factor B, Orai1: Protein abundance of Ca2+ release activated channel moiety (CRAC), STIM1: Ca2+ sensing proteins, NMDAR/NO: N-methyl-D-aspartate receptors/nitric oxide, ERK: Extracellular signal-regulated kinase, GSK3: Glycogen synthase kinase 3, Akt-1: Protein kinase B, BDNF: Brain-derived neurotrophic factor, CREB: Response element binding, $STAT1^{S727}$: Signal transducer and activator of transcription1 serin 727, $STAT3^{Y705}$: Signal transducer and activator of transcription3 tyrosin 705.

CONCLUSION

Lithium medication has significantly influenced behavior, neurochemistry, and physiology in laboratory animals. Lithium functions as a mood stabilizer, decreases hyperactivity and aggression, and exhibits neuroprotective qualities in models of brain injury and degeneration. However, prolonged exposure up to 8 weeks or high-dose exposure up to 200 mg/kg in mice can cause toxicity, including kidney damage, thyroid problems, and developmental defects. These findings confirmed lithium's therapeutic potential while emphasizing the need for careful dose and monitoring. In future studies, it is recommended to use *in vitro* application of lithium chloride on human cell lines in order to control glucose homeostasis and liver injury.

DECLARATIONS

Funding

This study was not supported financially and received no funding.

Ethical considerations

All authors reviewed potential ethical issues, including data falsification, multiple publication and submission, redundancy, plagiarism, consent to publish, and misconduct, before publication.

Acknowledgments

The authors would like to thank the Department of Pharmacology and Toxicology, Faculty of Pharmacy, Zagazig University, Egypt.

Authors' contributions

Marwa Ghamry developed the theoretical formalism, performed the analytic calculations, and performed the numerical simulations. Islam Ibrahim and Shimaa Elshazly contributed to editing the last version of the manuscript. Ahmed Fahmy supervised the project. All authors confirmed the last edition of the manuscript before submission to the journal.

Availability of data and materials

The data is available upon reasonable request from the corresponding author.

Competing interests

The authors confirmed that there is no conflict of interest.

REFERENCES

Albayrak A, Halici Z, Polat B, Karakus E, Cadirci E, Bayir Y, and Atamanalp SS (2013). Protective effects of lithium. A new look at an old drug with potential antioxidative and anti-inflammatory effects in an animal model of sepsis. International Immunopharmacology, 16(1): 35-40. DOI: https://www.doi.org/10.1016/j.intimp.2013.03.018

Alda M (2015). Lithium in the treatment of bipolar disorder. Pharmacology and pharmacogenetics. Molecular Psychiatry, 20(6): 661-670. DOI: https://www.doi.org/10.1038/mp.2015.4

Arciniegas Ruiz S, Rippin I, and Eldar-Finkelman H (2022). Prospects in GSK-3 signaling: From cellular regulation to disease therapy. Cells, 11(10): 1618. DOI: https://www.doi.org /10.3390/cells11101618

Balaram V, Santosh M, Satyanarayanan M, Srinivas N, and Gupta H (2024). A review of applications, occurrence, exploration, extraction, rercycling, analysis, and environmental impact. Geoscience Frontiers, 15(5): 101868. DOI: https://www.doi.org/10.1016/j.gsf.2024.101868

Bao H, Ge Y, Wang Z, Zhuang S, Dworkin L, Peng A, and Gong R (2014). Delayed administration of a single dose of lithium promotes recovery from AKI. Journal of the American Society of Nephrology, 25(3): 488-500. DOI: https://www.doi.org /10.1681/ASN.2013040350

Baumann P, Nil R, Souche A, Montaldi S, Baettig D, Lambert S, Uehlinger C, Kasas A, Amey M, and Jonzier-Perey M (1996). A double-blind, placebo-controlled study of citalopram with and without lithium in the treatment of therapy-resistant depressive patients: A clinical, pharmacokinetic, and pharmacogenetic investigation. Journal of Clinical Psychopharmacology, 16(4): 307-314. DOI: https://www.doi.org/10.1097/00004714-199608000-00006

Boivin E, Le Daré B, Bellay R, Vigneau C, Mercerolle M, and Bacle A (2023). Long-term lithium therapy and risk of chronic kidney disease, hyperparathyroidism and hypercalcemia. A cohort study. International Journal of Bipolar Disorders, 11(1): 4. DOI: https://www.doi.org/10.1186/s40345-023-00286-8

Brown ES (2009). Effects of glucocorticoids on mood, memory, and the hippocampus. Treatment and preventive therapy. Annals of the New York Academy of Sciences, 1179(1): 41-55. DOI: https://www.doi.org/10.1111/j.1749-6632.2009.04981.x

Brown KM and Tracy DK (2013). Lithium: The pharmacodynamic actions of the amazing ion. Therapeutic advances in psychopharmacology, 3(3): 163-176. https:// www.doi.org/10.1177/2045125312471963

Lowe H, Boswell J, Jackson B, Price-Arroyave J, and Ray SD (2023). Side effects of lithium. Side Effects of Drugs Annual, 45: 1-8. DOI: https://www.doi.org/10.1016/bs.seda.2023.09.001

Burillo J, Marqués P, Jiménez B, González-Blanco C, Benito M, and Guillén C (2021). Insulin resistance and diabetes mellitus in Alzheimer's disease. Cells, 10(5): 1236. DOI: https:// www.doi.org/10.3390/cells10051236

Chambers GRJ, Kerry, and Owen G (1977). Lithium used with a diuretic. British Medical Journal, 2(6090): 805-806. DOI: https://www.doi.org/10.1136/bmj.2.6090.805-a

Chen B, Zhang M, and Ji M (2022). The neuroprotective mechanism of lithium after ischaemic stroke. Communications Biology, 5: 105. DOI: https://www.doi.org/10.1038/s42003-022-03051-2

Chevalier N, Guillou P, Viguié C, Fini JB, Sachs LM, Michel-Caillet C, and Mhaouty-Kodja S (2024). Lithium and endocrine disruption: A concern for human health?. Enviromental International, 190: 108861. DOI: https://www.doi.org/10.1016/j.envint.2024.108861

Chiu C and Chuang D (2011). Neuroprotective action of lithium in disorders of the central nervous system. Medical Sciences, 36(6): 461-476. DOI: https://www.doi.org/10.3969/j.issn.1672-7347.2011.06.001

Chuang DM, Wang Z, and Chiu CT (2011). GSK-3 as a target for lithium-induced neuroprotection against excitotoxicity in neuronal cultures and animal models of ischemic stroke. Frontiers in Molecular Neuroscience, 4: 15. DOI: https://www.doi.org/10.3389/fnmol.2011.00015

Contestabile A, Greco B, Ghezzi D, Tucci V, Benfenati F, and Gasparini L (2013). Lithium rescues synaptic plasticity and memory in Down syndrome mice. Journal of Clinical Investigation, 123(1): 348-361. DOI: https://www.doi.org/10.1172/JCI64650

Damiano RF, Loureiro JC, Pais MV, Pereira RF, Corradi MDM, Di SantiT, and Forlenza OV (2023). Revisiting global cognitive and functional state 13 years after a clinical trial of lithium for mild cognitive impairment. Brazilian Journal of Psychiatry, 45(1): 46-49. DOI: https://www.doi.org/10.47626/1516-4446-2022-2767.

Dangana EO, MichaelO S, OmolekuloTE, AreolaED, and Olatunji LA (2019). Enhanced hepatic glycogen synthesis and suppressed adenosine deaminase activity by lithium attenuates hepatic triglyceride accumulation in nicotine-exposed rats. Biomedicine & Pharmacotherapy, 109: 1417-1427. DOI: https://www.doi.org/10.1016/j.biopha.2018.10.067

Delangre E, Liu J, Tolu S, Maouche K, Armanet M, Cattan P, Pommier G, Bailbé D, and Movassat J (2021). Underlying mechanisms of glucocorticoid-induced β-cell death and dysfunction. A new role for glycogen synthase kinase 3. Cell Death & Disease, 12: 1136. DOI: https://www.doi.org/10.1038/s41419-021-04419-8

Delangre E, Pommier G, Tolu S, Uzan B, Bailbé D, and Movassat J (2023). Lithium treatment mitigates the diabetogenic effects of chronic cortico-therapy. Biomedicine & Pharmacotherapy, 164: 114895. DOI: https://www.doi.org/10.1016/j.biopha.2023.114895

Dell'Osso L, Del Grande C, Gesi C, Carmassi C, and Musetti L (2016). A new look at an old drug. Neuroprotective effects and therapeutic potentials of lithium salts. Neuropsychiatric Disease and Treatment, 12: 1687-1703. DOI: https://www.doi.org/10.2147/NDT.S106479

Dong BT, Tu GJ, Han YX, and Chen Y (2015). Lithium enhanced cell proliferation and differentiation of mesenchymal stem cells to neural cells in rat spinal cord. International Journal of Clinical and Experimental Pathology, 8(3): 2473-2483. DOI: https://pmc.ncbi.nlm.nih.gov/articles/PMC4440062/

Dousa TP and Barnes LD (1976). Lithium-induced diuretic effect of antidiuretic hormone in rats. The American Journal of Physiology, 231(6): 1754-1759. DOI: https://www.doi.org/10.1152/ajplegacy.1976.231.6.1754

Eldar-Finkelman H (2002). Glycogen synthase kinase 3. An emerging therapeutic target. Trends in Molecular Medicine, 8(3): 126-132. DOI: https://www.doi.org/10.1016/s1471-4914(01)02266-3

Eraslan E, Matur E, Akyol S, Ekiz EE, Akyazı İ, Bala, Deniz A, Gürsel FE, and Dariyerli N (2024). Impact of chronic lithium treatment on brain oxidative stress and anxiety-like behaviors in rats: Dose-dependent effects. General Physiology & Biophysics, 43(3): 263: 271. DOI: https://www.doi.org/10.4149/gpb_2024006

Ghanaatfar F, GhanaatfarA, Isapour P, Farokhi N, Bozorgniahosseini S, Javadi M, Gholami, M, Ulloa L, Coleman-Fuller N, and Motaghinejad M (2023). Is lithium neuroprotective? An updated mechanistic illustrated review. Fundamental & Clinical Pharmacology, 37(1): 4-30. DOI: https://www.doi.org/10.1111/fcp.12826

Gitlin M (2016). Lithium side effects and toxicity: Prevalence and management strategies. International Journal of Bipolar Disorders, 4: 27. DOI: https:// www.doi.org/10.1186/s40345-016-0068-y

Göttert R, Fidzinski P, Kraus L, Schneider U C, Holtkamp M, Endres M, Gertz K, and Kronenberg G (2022). Lithium inhibits tryptophan catabolism via the inflammation-induced kynurenine pathway in human microglia. Glia, 70(3): 558-571. DOI: https://www.doi.org/10.1002/glia.24123.

Gould T, Chen G, and Manji, H (2004). *In Vivo* Evidence in the Brain for Lithium Inhibition of Glycogen Synthase Kinase-3. Neuropsychopharmacology, 29: 32-38. DOI: https://www.doi.org/10.1038/sj.npp.1300283

Hamstra SI, Roy BD, Tiidus P, MacNeil AJ, Klentrou P, MacPherson REK, and Fajardo VA (2023). Beyond its psychiatric use: The benefits of low-dose lithium supplementation. Current Neuropharmacology, 21(4): 891-910. DOI: https://www.doi.org/10.2174/1570159X20666220302151224

Henriksen EJ and Dokken BB (2006). Role of glycogen synthase kinase-3 in insulin resistance and type 2 diabetes. Current Drug Targets, 7(11): 1435-1441. DOI: https://www.doi.org/10.2174/1389450110607011435

Henriksen EJ and Teachey MK (2007). Short-term *in vitro* inhibition of glycogen synthase kinase 3 potentiates insulin signaling in type I skeletal muscle of Zucker diabetic fatty rats. Metabolism, 56(7): 931-938. DOI: https://www.doi.org/10.1016/j.metabol.2007.03.002

Jafari RM, Ghahremani MH, Rahimi N, Shadboorestan A, Rashidian A, Esmaeili J, Mehr SE, Dehpour AR (2018). The anticonvulsant activity and cerebral protection of chronic lithium chloride via NMDA receptor/nitric oxide and phospho-ERK. Brain Research Bulletin, 137: 1-9. DOI: https://www.doi.org/10.1016/j.brainresbull.2017.10.015

Jung S, Koh J, Kim S, and Kim K (2017). Effect of lithium on the mechanism of glucose transport in skeletal muscles. Journal of Nutritional Science and Vitaminology, 63(6): 365-371. DOI: https://www.doi.org/10.3177/jnsv.63.365

Jung S, Koh J, Kim S, and Kim K (2017). Effect of lithium on the mechanism of glucose transport in skeletal muscles. Journal of Nutritional Science and Vitaminology, 63(6): 365-371. DOI: https://www.doi.org/10.3177/jnsv.63.365

Khan MS, Ali T, Abid MN, Jo MH, Khan A, Kim MW, Yoon GH, Cheon EW, Rehman SU, and Kim MO (2017). Lithium ameliorates lipopolysaccharide-induced neurotoxicity in the cortex and hippocampus of the adult rat brain. Neurochemistry International, 108: 343-354. DOI: https://www.doi.org/10.1016/j.neuint.2017.05.008

Lau YK, Peck SH, Arginteanu T, Wu M, Lin M, Shore EM, Klein PS, Casal ML, and Smith LJ (2022). Effects of lithium administration on vertebral bone disease in mucopolysaccharidosis I dogs. Bone, 154: 116237. DOI: https://www.doi.org/10.1016/j.bone.2021.116237

Lazarus JH (2009). Lithium and thyroid. Best Practice & Research Clinical Endocrinology & Metabolism, 23(6): 723-733. DOI: https://www.doi.org/10.1016/j.beem.2009.06.002

Lee TM, Lin SZ, and Chang NC (2014). Antiarrhythmic effect of lithium in rats after myocardial infarction by activation of Nrf2/HO-1 signaling. Free Radical Biology & Medicine, 77: 71-81. DOI: https://www.doi.org/10.1016/j.freeradbiomed.2014.08.022.

Li H, Huang K, Liu X, Liu J, Lu X, Tao K, Wang G, and Wang J (2014). Lithium chloride suppresses colorectal cancer cell survival and proliferation through ROS/GSK-3β/NF-κB signaling pathway. Oxidative Medicine and Cellular Longevity, 2014: 241864. DOI: https://www.doi.org/10.1155/2014/241864

Lieber I, Ott M, Öhlund L, Lundqvist R, Eliasson M, Sandlund M, and Werneke U (2020). Lithium-associated hypothyroidism and potential for reversibility after lithium discontinuation: Findings from the LiSIE retrospective cohort study. Journal of Psychopharmacology, 34(3): 293-303. DOI: https://www.doi.org/10.1177/0269881119882858

Liu A, Fang H, Dahme U, and Dirsch O (2013). Chronic lithium treatment protects against liver ischemia/reperfusion injury in rats. Liver Transplantation, 19(7): 762-772. DOI: https://www.doi.org/10.1002/lt.23666

Machado-Vieira R, Manji HK, and Zarate CA Jr (2009). The role of lithium in the treatment of bipolar disorder: Convergent evidence for neurotrophic effects as a unifying hypothesis. Bipolar Disorder, 2(Suppl 2): 92-109. DOI: https://www.doi:10.1111/j.1399-5618.2009.00714.x

Marshall TM (2015). Lithium as a nutrient. Journal of American Physicians and Surgeons, 20(4): 104-109. DOI: https://www.jpands.org/vol20no4/marshall.pdf?crsi=662497726

Mathur A, Pandey VK, and Kakkar P (2017). PHLPP: A putative cellular target during insulin resistance and type 2 diabetes. Journal of Endocrinology, 233(3): R185-R198. DOI: https:// www.doi.org/10.1530/JOE-17-0081

Matur E, Akyol S, Toplan S, Ozdemir S, Akyazı I, and Darıyerli N (2025). Impact of lithium on the immune system. An investigation of T-Cell subpopulations and cytokine responses in rats. Biological Trace Element Research, 203(2): 944-952. DOI: https://www.doi.org/10.1007/s12011-024-04202-8

Medić B, Stojanović M, Stimec BV, Divac N, Vujović KS, Stojanović R, Čolović M, Krstić D, and Prostran M (2020). Lithium - Pharmacological and toxicological aspects: The current state of the art. Current Medicinal Chemistry, 27(3): 337-351. DOI: https://www.doi.org/10.2174/0929867325666180904124733

Mehrafza S, Kermanshahi S, Mostafidi S, Motaghinejad M, Motevalian M, and Fatima S (2019). Pharmacological evidence for lithium-induced neuroprotection against methamphetamine-induced neurodegeneration via Akt-1/GSK3 and CREB-BDNF signaling pathways. Iranian Journal of Basic Medical Sciences, 22(8): 856-865. DOI: https://www.doi.org/10.22038/ijbms.2019.30855.7442

Mohammad JR, Ghahremani MH, Rahimi N, Shadboorestan A, Rashidian A, Esmaeili J, Ejtemaei MS, and Dehpour AR (2018). The anticonvulsant activity and cerebral protection of chronic lithium chloride via NMDA receptor/nitric oxide and phospho-ERK. Brain Research Bulletin, 137: 1-9. DOI: https://www.doi.org/10.1016/j.brainresbull.2017.10.015

Musik I, Kocot J, and Kiełczykowska M (2015). Effect of sodium selenite on chosen anti- and pro-oxidative parameters in rats treated with lithium: A pilot study. Pharmacological Reports, 67(3): 446-450. DOI: https://www.doi.org/10.1016/j.pharep.2014.11.010

Nassar A and Azab AN (2014). Effects of lithium on inflammation. ACS Chemical Neuroscience, 5(6): 451-458. DOI: https://www.doi.org/10.1021/cn500038f

Nery LR, Eltz NS, Hackman C, Fonseca R, Altenhofen S, Guerra HN, Freitas VM, Bonan CD, and Vianna MR (2014). Brain intraventricular injection of amyloid-β in zebrafish embryo impairs cognition and increases tau phosphorylation, effects reversed by lithium. PloS One, 9(9): e105862. DOI: https://www.doi.org/10.1371/journal.pone.0105862

Noguchi KK, Johnson SA, Kristich LE, Martin LD, Dissen GA, Olsen EA, Olney JW, and Brambrink AM (2016). Lithium protects against Anaesthesia neurotoxicity in the infant primate brain. Scientific Reports, 6: 22427. DOI: https://www.doi.org/10.1038/srep22427

Nygren MK, Døsen G, Hystad ME, Stubberud H, Funderud S, and Rian E (2011). Wnt3A activates canonical Wnt signalling in acute lymphoblastic leukaemia (ALL) cells and inhibits the proliferation of B-ALL cell lines. British Journal of Haematology, 136(3): 400-413. DOI: https://www.doi.org/10.1111/j.1365-2141.2006.06442.x

Oruch R, Elderbi MA, Khattab HA, Pryme IF, and Lund A (2014). Lithium: A review of pharmacology, clinical uses, and toxicity. European Journal of Pharmacology, 740: 464-473. DOI: https://www.doi.org/10.1016/j.ejphar.2014.06.042

Ostrovskaya RU, Ivanov SV, and Durnev AD (2018). Neuroprotective lithium salts protect pancreatic β-cells from damage. Bulletin of Experimental Biology and Medicine, 165(6): 758-762. DOI: https://www.doi.org/10.1007/s10517-018-4259-7

Pitasi CL, Liu J, Gausserès B, Pommier G, Delangre E, Armanet M, and Movassat J (2020). Implication of glycogen synthase kinase 3 in diabetes-associated islet inflammation. Journal of Endocrinology, 244(1): 133-148. DOI: https://www.doi.org/10.1530/JOE-19-0239

Puglisi-Allegra S, Ruggieri S, and Fornai F (2021). Translational evidence for lithium-induced brain plasticity and neuroprotection in the treatment of neuropsychiatric disorders. Transl Psychiatry, 11(1): 366-372. DOI: https://www.doi:10.1038/s41398-021-01492-7

Rana AK, Sharma S, Patial V, and Singh D (2022). Lithium therapy subdues neuroinflammation to maintain pyramidal cells arborization and rescues neurobehavioural impairments in ovariectomized rats. Molecular Neurobiology, 59(3): 1706-1723. DOI: https://www.doi.org/10.1007/s12035-021-02719-w

Rana AK and Singh D (2018). Targeting glycogen synthase kinase-3 for oxidative stress and neuroinflammation. Opportunities, challenges and future directions for cerebral stroke management. Neuropharmacology, 139: 124-136. DOI: https://www.doi.org/10.1016/j.neuropharm.2018.07.006

Richard SA (2024). Elucidating the pivotal molecular mechanisms, therapeutic and neuroprotective effects of lithium in traumatic brain injury. Brain and Behavior, 14(6): e3595. DOI: https://www.doi.org/10.1002/brb3.3595

Rizk M, Saker Z, Harati H, Fares Y, Bahmad HF, and Nabha S (2021). Deciphering the roles of glycogen synthase kinase 3 (GSK3) in the treatment of autism spectrum disorder and related syndromes. Molecular Biology Reports, 48: 2669-2686. DOI: https://www.doi.org/10.1007/s11033-021-06237-9

Rowe MK and Chuang DM (2004). Lithium neuroprotection: Molecular mechanisms and clinical implications. Expert Reviews in Molecular Medicine, 6(21): 1-18. DOI: https://www.

Rybakowski JK (2022). Antiviral, immunomodulatory, and neuroprotective effect of lithium. Journal of Integrative Neuroscience, 21(2): 68. DOI: https://www.doi.org/10.31083/j.jin2102068

Rybakowski JK (2020). Lithium–past, present, future. International Journal of psychiatry in Clinical Practice, 24(4): 330-340. DOI: https://www.doi.org/10.1080/13651501.2020.1775855

Schleicher SB, Zaborski JJ, Riester R, Zenkner N, Handgretinger R, Kluba T, Traub F, and Boehme KA (2017). Combined application of arsenic trioxide and lithium chloride augments viability reduction and apoptosis induction in human rhabdomyosarcoma cell lines. PloS One, 12(6): e0178857. DOI: https://www.doi.org/10.1371/journal.pone.0178857

Schoretsanitis G, De Filippis R, Brady BM, Homan P, Suppes T, and Kane JM (2022). Prevalence of impaired kidney function in patients with long-term lithium treatment. A systematic review and meta-analysis. Bipolar Disorders, 24(3): 264-274. DOI: https://www.doi.org/10.1111/bdi.13154

Schrauzer GN (2002). Lithium: Occurrence, dietary intakes, nutritional essentiality. Journal of the American College of Nutrition, 21(1): 14-21. DOI: https://www.doi.org/10.1080/07315724.2002.10719188.

Singh G, Magny S, Singh H, Singh S, and Virk IS (2023). Differentiating between lithium tremors and extrapyramidal tremors in a patient on long-term antipsychotics and lithium medication. Cureus, 15(7): e42406. DOI: https://www.doi.org/10.7759/cureus.42406

Sinha D, Wang Z, Ruchalski KL, Levine JS, Krishnan S, Lieberthal W, Schwartz JH, and Borkan SC (2005). Lithium activates the Wnt and phosphatidylinositol 3-kinase Akt signaling pathways to promote cell survival in the absence of soluble survival factors. American Journal of Physiology-Renal Physiology, 288(4): 703-713. DOI: https://www.doi.org/10.1152/ajprenal.00189.2004

Smith E, Coetzee GA, and Frenkel B (2002). Glucocorticoids inhibit cell cycle progression in differentiating osteoblasts via glycogen synthase kinase-3beta. Journal of Biological Chemistry, 277(20): 18191-18197. DOI: https://www.doi.org/10.1074/jbc.M109708200

Su H, Yuan Q, Qin D, Yang X, Wong WM, So KF, and Wu W (2014). Lithium enhances axonal regeneration in peripheral nerve by inhibiting glycogen synthase kinase 3β activation. BioMed Research International, 2014: 658753. DOI: https://www.doi.org/10.1155/2014/658753.

Sukkar B, Hauser S, Pelzl L, Hosseinzadeh Z, Sahu I, Al-Maghout T, Bhuyan AAM, Zacharopoulou N, Stournaras C, Schöls L et al. (2018). Inhibition of lithium sensitive orai1/ STIM1 expression and store operated Ca2+ entry in chorea-acanthocytosis neurons by NF-κB inhibitor wogonin. Cellular Physiology and Biochemistry, 51(1): 278-289. DOI: https:// www.doi.org/10.1159/000495229

Sun XB, Lu HE, Chen Y, Fan XH, and Tong B (2014). Effect of lithium chloride on endoplasmic reticulum stress-related PERK/ROCK signaling in a rat model of glaucoma. Die Pharmazie, 69(12): 889-893. DOI: http://www.doi.org/10.1691/ph.2014.4672

Vallée A, Vallée JN, and Lecarpentier Y (2021). Parkinson's disease: Potential actions of lithium by targeting the WNT/β-catenin pathway, oxidative stress, inflammation and glutamatergic pathway. Cells, 10(2): 230. DOI: https://www.doi.org/10.3390/cells10020230

Youngs RM, Chu MS, Meloni EG, Naydenov A, Carlezon WA Jr, and Konradi C (2006). Lithium administration to preadolescent rats causes long-lasting increases in anxiety-like behavior and has molecular consequences. The Journal of Neuroscience, 26(22): 6031-6039. DOI: https://www.doi.org/10.1523/jneurosci.0580-06.2006

Yu F, Wang Z, Tchantchou F, Chiu CT, Zhang Y, and Chuang DM (2012). Lithium ameliorates neurodegeneration, suppresses neuroinflammation, and improves behavioral performance in a mouse model of traumatic brain injury. Journal of Neurotrauma, 29(2): 362-374. DOI: https://www.doi.org/10.1089/neu.2011.1942

Zanandrea R, Abreu MS, Piato A, Barcellos LJG, and Giacomini ACVV (2018). Lithium prevents scopolamine-induced memory impairment in zebrafish. Neuroscience Letters, 664: 34-37. DOI: https:// www.doi.org/10.1016/j.neulet.2017.11.010

Zeng Z, Haitao W, Fu Sh, Lihua Z, Peter L, Remi Q, and Wen HZ (2016). Lithium Ions attenuate serum-deprivation-induced apoptosis in Pc12 cells through regulation of the Akt/Foxo1 signaling pathways. Psychopharmacology, 233: 785-94. DOI: https://www.doi.org/10.1007/s00213-015-4168-7

Zhang J, Anshul F, Malhotra DK, Jaume J, Dworki LD, and Gong R (2021). Microdose lithium protects against pancreatic islet destruction and renal impairment in streptozotocin-elicited diabetes. Antioxidants, 10(1): 138. DOI: https://www.doi.org/10.3390/antiox10010138.

Zhao YJ, Qiao H, Liu DF, Li J, Li JX, Chang SE, Lu T, Li FT, Wang D, Li HP et al. (2022). Lithium promotes recovery after spinal cord injury. Neural Regeneration Research, 17(6): 1324-1333. DOI: https://www.doi.org/10.4103/1673-5374.327348.

Zheng Z, Ma H, Zhang X, Tu F, Wang X, Ha T, Fan M, Liu L, Xu J, Yu K et al. (2017). Enhanced glycolytic metabolism contributes to cardiac dysfunction in polymicrobial sepsis. The Journal of Infectious Diseases, 215(9): 1396-1406. DOI: https://www.doi.org/10.1093/infdis/jix138

Zhu Z, Yin J, Guan J, Hu B, Niu X, Jin D, Wang Y, and Zhang C (2014). Lithium stimulates human bone marrow derived mesenchymal stem cell proliferation through GSK-3β-dependent β-catenin/Wnt pathway activation. The FEBS Journal, 281(23): 5371-5389. DOI: https://www.doi.org/10.1111/febs.13081.