

REVIEW

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Lithium and neuroprotection: a review of molecular targets and biological effects at subtherapeutic concentrations in preclinical models of Alzheimer's disease

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Abstract

Background Experimental studies consistently demonstrate that lithium modulates multiple intracellular signaling pathways involved in crucial neurobiological responses, highlighting its therapeutic potential in degenerative diseases. Lithium has demonstrated significant neuroprotective potential in preclinical models of Alzheimer's disease (AD) and other neurodegenerative disorders.

Contents This review examines the molecular mechanisms and biological effects of lithium at subtherapeutic concentrations, focusing on its ability to modulate key intracellular pathways, such as the inhibition of glycogen synthase kinase-3 beta (GSK-3 β), reduction of Tau hyperphosphorylation, and enhancement of neurotrophic and anti-inflammatory responses. Evidence from animal and cellular studies underscores lithium's ability to reduce amyloid plaques, maintain neuronal integrity, improve memory, and decrease neuroinflammation, even at doses much lower than those used clinically for mood stabilization.

Conclusion Evidence from animal and cellular models indicates that subtherapeutic lithium doses may provide a safer and more practical approach to neuroprotection, particularly in AD. However, further research is necessary to optimize dosing strategies, assess long-term safety, and translate these findings into clinical applications.

Keywords Lithium, Neuroprotection, Alzheimer's disease, Dementia, Neurodegenerative diseases

Background

The use of lithium as a therapeutic agent has evolved significantly over the decades, particularly in the context of neuroprotection. Initially recognized for its mood-stabilizing properties in psychiatric disorders, research has increasingly focused on its potential neuroprotective

capabilities, suggesting that it may play a role in mitigating neuronal damage associated with various neurological conditions (Almeida et al. 2022; Gitlin and Bauer 2024; Singulani et al. 2024). For example, research examining trace lithium levels in groundwater indicates that continuous consumption of lithium-rich water, even at minimal concentrations, may diminish the need for psychiatric hospitalizations, reduce suicide rates, and ultimately offer protective benefits against dementia (Oenning et al. 2018). Lithium has, therefore, emerged as a promising candidate for neuroprotection, particularly in AD (Lu et al. 2024). Its multifaceted effects on

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biological and molecular pathways, brain structure, and various cognitive functions have been extensively studied, especially in preclinical models, yielding valuable insights into its neuroprotective potential, although the relationship between these effects and brain lithium concentrations remains unclear (Strawbridge and Young 2024).

A study investigating chronic lithium microdose treatment has shown that lithium effectively prevents memory loss and neurological changes associated with AD, particularly by reducing senile plaques and increasing BDNF density in the cerebral cortex (Leyhe et al. 2009). This has prompted further investigation into subtherapeutic dosing and its implications for clinical practice, as evidence suggests that lower doses may still retain efficacy in providing neuroprotection, albeit with diminishing strength of evidence as doses decrease (Quiroz et al. 2010; Rybakowski et al. 2018). Moreover, prolonged lithium administration has been demonstrated to activate phospholipase A2 (PLA2) in the brain, correlating with improved memory retrieval. Extremely low doses of lithium, up to 400 times lower than conventional clinical doses, exhibit remarkable potential in alleviating AD and enhancing cognitive functions while causing minimal adverse effects (Strawbridge and Young 2024).

Mechanism of action

The primary molecular targets of lithium include glycogen synthase kinase-3 beta (GSK-3 β), inositol monophosphatase (IMPase), and the mammalian target of rapamycin (mTOR). Lithium acts as a potent dual inhibitor of GSK-3 β , a proline-directed serine-threonine kinase that serves as a crucial hub in intracellular signaling (Fenech et al. 2023; Mendes et al. 2009; Monaco et al. 2018) due to its numerous regulatory loops and downstream effects (Peineau et al. 2008). The inhibition of GSK-3 β prevents the phosphorylation of key substrates, including glycogen synthase, microtubule-associated proteins such as MAP1B and Tau, presenilin-1, CREB, and beta-catenin. This interference affects several physiological processes, including energy metabolism, neural cell development, neuronal plasticity, and gene regulation (Klein and Melton 1996; Lau et al. 1999). Overactive GSK-3 β significantly contributes to the pathogenesis of AD by promoting the excessive production of amyloid- β peptide and the hyperphosphorylation of Tau, both of which are linked to the formation of senile plaques and neurofibrillary tangles—key pathological features of AD (Hooper et al. 2008). Furthermore, lithium has been shown to enhance the synthesis and release of brain-derived neurotrophic factor (BDNF) (De-Paula et al. 2016a, b; Leyhe et al. 2009), thereby supporting neuronal communication, survival, and synaptic plasticity, all essential for preserving cognitive health. Additionally,

lithium is known to enhance mitochondrial function (Singulani et al. 2021) and assist in telomere maintenance (Cardillo et al. 2018; Martinsson et al. 2013), thus reducing telomere shortening and promoting cellular integrity.

Preclinical research demonstrates significant variability in lithium dosing across studies using cell culture and animal models. Working concentrations vary from micromolar to doses 5 to 10 times higher than the therapeutic reference set for humans (Fenech et al. 2023). This variability affects the intrinsic characteristics of the experimental model and limits the duration of trials, as the emergence of toxic effects often prevents the evaluation of long-term outcomes (Gao et al. 2016).

Conventional lithium formulations have a narrow therapeutic window and are associated with a severe side effect profile, which includes renal toxicity, thyroid disorders, tremors, nausea, fatigue, hyperphagia, hypercalcemia, and an increased white blood cell count (Gitlin 2016). The risk of toxicity is mitigated by using subtherapeutic doses, which prevent elevated serum concentrations. This strategy may present a more favorable safety profile, allowing the investigation of lithium's neuroprotective properties without the hazards typically associated with elevated therapeutic levels (Wraae 1978). Consequently, it is essential to examine how these lower doses influence specific brain structures, including the cerebral cortex, hippocampus, and striatum, to optimize the clinical efficacy of lithium while ensuring its safe application in neuroprotection.

Methods

The primary objective of this review was to assess the efficacy of subtherapeutic lithium dosages as a potential pharmaceutical intervention in both animal and cellular models of AD, with a particular focus on their ability to slow disease progression and enhance cognitive function. To achieve this goal, a comprehensive bibliographic search was conducted using the PubMed platform to identify relevant publications available until May 2024. The search parameters were restricted to English-language articles with no limitations on publication dates. Search terms included (lithium) AND (low OR micro OR subtherapeutic) AND (Alzheimer's disease), filtering for "animal studies." A second search was conducted to include (cellular OR cell) AND (models OR studies). The authors exclusively selected original studies that investigated the neurobiological effects of lithium at subtherapeutic concentrations (micro and low doses of lithium).

The selected studies were systematically analyzed utilizing Biblioshiny, a bibliometric analysis tool developed within the R programming environment, to facilitate scientific mapping. It helps researchers analyze and summarize large amounts of research information in an organized way by studying patterns in publications,

such as which topics are covered the most or how articles connect, which are displayed in easy-to-understand graphs and diagrams, as well as word clouds derived from the most prevalent terms in abstracts and keywords, thus enabling the identification of overarching themes without redundancy across studies.

Results

Of the 25 manuscripts identified through the search, thirteen met the inclusion criteria for this review. Among these, nine studies utilized animal models, while five used cellular models. Variations in lithium dosage and administration durations were noted across the studies, as illustrated in Fig. 1. The lithium concentrations used in cellular investigations ranged from 2 $\mu\text{g}/\text{ml}$ to 200 $\mu\text{g}/\text{ml}$, with the most frequently examined dosages being 2 $\mu\text{g}/\text{ml}$, 20 $\mu\text{g}/\text{ml}$, and 200 $\mu\text{g}/\text{ml}$. These explorations clarify the influence of lithium on neuroprotective cellular pathways in a dose-dependent manner. In animal studies, lithium was administered to rats or mice through their drinking water or food. The dosages incorporated into the food included 4 $\mu\text{g}/\text{kg}$, 1 mg/kg, 1.2 mg/kg, 2 mg/kg, and 10 mg/kg. The lithium concentrations in drinking water were 125 $\mu\text{g}/\text{ml}$ and 1.25 mg/ml, respectively. This diverse range of methodologies facilitated a comprehensive investigation of lithium's effects across various dosage levels and administration routes. Tables 1 and 2

show data from studies in animal and cellular models of AD, including lithium dosages, treatment duration, and primary outcomes.

Discussion

Animal models

Animal models are widely used in investigating AD, yielding critical insights into the pathology, pharmacology, and behavioral changes associated with the condition (Quiroz et al. 2010; Methaneethorn 2018). Effectively translating findings from these models into clinical applications for humans requires a meticulous approach that considers the specific characteristics of each model. In rodents, lithium is rapidly absorbed from the gastrointestinal tract, distributed throughout total body water without binding to plasma proteins, and is almost exclusively eliminated by the kidneys (Wood et al. 1986; Wraae 1978). In rats, lithium serum concentrations peak approximately one hour after the administration of a 2 mmol/kg dose (Ebadi et al. 1974). In the brain, peak concentrations occur within 4 to 6 h (Wraae 1978), corresponding to approximately 40% of peak serum levels (Mukherjee et al. 1976). The half-life of lithium in serum ranges from 8 to 10 h, while in the brain, it extends to 24 to 36 h (Ebadi et al. 1974; Martinsson et al. 2013; Mukherjee et al. 1976). These pharmacokinetic differences highlight the importance of dose adjustments and

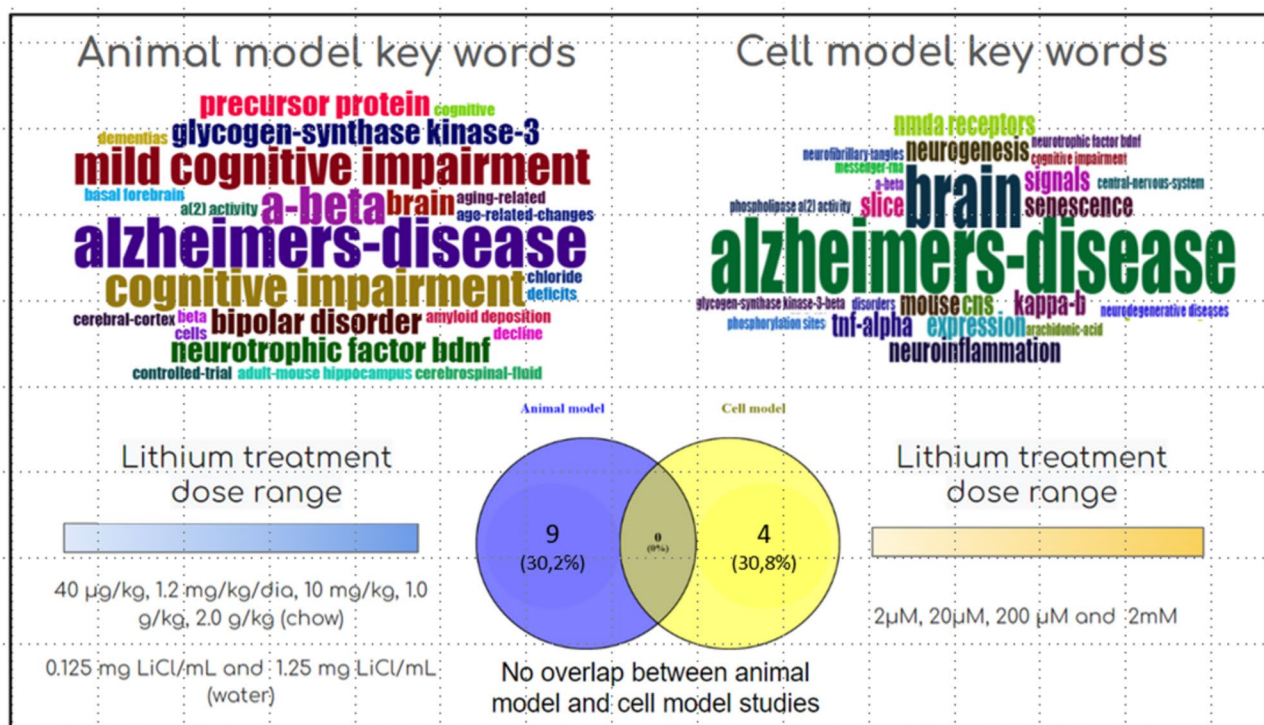


Fig. 1 The word cloud represents the keywords in the 13 articles selected for analysis and discussion. The Venn diagram shows the final number of papers, and the bars represent the range of doses used in animal and cell culture models. All concentrations were converted into μM and mM

Table 1 Studies in animal models for AD

Animal model	Dose and duration of treatment	Results	Reference
Male Wistar rats (8–10 weeks).	0.125 mg/ml and 1.25 mg /ml for 100 days.	Increase sPla2 compared to controls	Mury et al. 2016
Male C57BL/6J mice.	10 mg/kg/day for 6 or 12 weeks.	Reduced GSK3 activity in the prefrontal cortex.	Fenech et al. 2023
3xTg-AD mice.	1.0 and 2.0 g/kg for 34 weeks	Increase in CA1 neuron number.	Schaeffer et al. 2017
Transgenic mice (Cg-Tg (PDGFB-APPswind))	1.2 mg/Kg/day for 16 or 8 months.	Decreased senile plaques and increased BDNF in the cortex compared to non-treated transgenic mice.	Nunes et al. 2015
McGill-R-Thy1-APP transgenic rats	40 µg/kg for 8 weeks.	Inactivation of GSK-3β, reduced BACE1 expression and activity and reduced amyloid levels.	Wilson et al. 2017
SAMP-8 and SAMP-8 mice.	1.5 mg/ Kg for 10 months.	Promoted memory maintenance, reduction in anxiety and maintenance of proteins related to memory formation and neuronal density; reduction of senile plaques density; increase in gamma-aminobutyric acid A (GABA) and α7 nicotinic cholinergic receptors density.	Pereira et al. 2024
McGill-R-Thy1-APP transgenic rats.	40 µg/kg and 1 ml/kg for 12 weeks.	Improvement of functional deficits in object recognition; loss of cholinergic boutons in the hippocampus, levels of soluble and insoluble cortical Aβ42 and hippocampal Aβ plaque number were reduced	Wilson et al. 2020
Triple-transgenic mouse model of AD (3x-TgAD)	1.0 g/kg and 2.0 g/kg for 34 weeks.	Positive regulation of protein localization to the membrane; protein localization to the cell periphery; oligodendrocyte differentiation, and regulation of protein localization to the plasma membrane.	Rocha et al. 2020
Triple-transgenic mouse model (3xTg-AD)	1.0 g/kg and 2.0 g/kg for 34 weeks.	Chronic lithium treatment was associated with longer hippocampus and parietal cortex telomeres.	Cardillo et al. 2018

considering species-specific characteristics to accurately extrapolate preclinical findings to clinical practice (Wraae 1978).

Mury et al. (2016) demonstrated that chronic administration of lithium at a dose of 2 mmol/kg increased phospholipase A2 (PLA₂) activity in the brain, particularly in the cortex and hippocampus. The activation of brain PLA₂, an enzyme critical for lipid signaling and membrane remodeling, constitutes a key mechanism through which lithium enhances memory performance in rodent models. This finding suggests that subtherapeutic doses of lithium promote the production of bioactive lipids that directly facilitate synaptic plasticity and cognitive function.

Glycogen synthase kinase-3 beta (GSK3β), a central enzyme involved in tau phosphorylation and amyloid precursor protein (APP) processing, is another pivotal target modulated by lithium. Subtherapeutic doses of lithium (0.2 mmol/kg/day) decrease GSK3β activity in key brain regions, including the hippocampus and prefrontal cortex (Fenech et al. 2023). This reduction in GSK3β activity directly correlates with diminished tau hyperphosphorylation and plays a crucial role in attenuating amyloidogenic APP processing—both processes being critical hallmarks of AD pathology. Furthermore, long-term administration of lithium (2 mmol/kg/day for 4 months) has been shown to preserve the CA1 pyramidal cell layer in 3xTg-AD mice by decreasing neuronal loss (Schaeffer et al. 2017). The neuroprotective pathway is similarly effective in maintaining the integrity of the CA1 pyramidal cell layer, thereby reducing cell loss. Structural preservation of the hippocampus, a region essential for memory and learning, has also been documented with subtherapeutic lithium treatment. In an obesity model, lithium supplementation has been observed to decrease GSK3 activity and enhance insulin sensitivity, indicating potential broader metabolic implications (Fenech et al. 2023).

Lithium administration has been shown to reduce markers associated with oxidative stress, thereby contributing to its neuroprotective effects. Additionally, varying doses of lithium treatment have decreased oxidative stress markers, further supporting these neuroprotective outcomes (Schaeffer et al. 2017). Lithium increases the levels of calcium/calmodulin-dependent protein kinase II (CaMKII) and BDNF, both of which are critical for memory formation, neuronal survival, and synaptic resilience. Beyond its biological benefits, the impact of lithium on behavioral and cognitive outcomes is substantial. Notably, Nunes et al. (2015) found that long-term administration of subtherapeutic doses of lithium (0.25 mmol/kg/day over 8 weeks) resulted in the reduction of neurofibrillary tangles and amyloid plaques in a transgenic mouse model of AD.

Table 2 Studies in cellular models for AD

Cell model	Dose and duration of treatment	Results	Reference
Organotypic hippocampal cultures (SAMP-8 mice)	2 μ M, 20 μ M and 200 μ M for 10 days.	Reduced neuronal loss and neuroinflammation in older individuals; significant reduction in the CA2 area of the hippocampus; reduction in the activation of NFkB and inflammatory cytokines densities, even in very low doses.	Toricelli et al. 2021
Primary cultures of cortical and hippocampal neurons.	0.02 mM, 0.2 mM, and 2 mM for 7 days.	Increased membrane phospholipid metabolism in cortical and hippocampal neurons by activating total, c- and iPLA ₂ .	De-Paula et al., 2015
Co-cultures of cortical and hippocampal neurons with glial cells	0.02 mM, 0.2 mM, and 2 mM for 7 days.	Secretion of pro- and anti-inflammatory interleukins in co-cultures of cortical and hippocampal neurons with glial cells.	De-Paula et al. 2016a, b
Primary cultures of cortical and hippocampal neurons	0.02 mM, 0.2 mM, and 2 mM for 7 days.	Consistent decrements in Akt and PKA in cortical neurons; increased protein expression of Akt and decreased PKA in hippocampal neurons.	De-Paula and Forlenza., 2022
Primary cultures of cortical neurons	0.02 mM, 0.2 mM, and 2 mM for 7 days.	Promotion of greater cell viability and preservation of neuronal telomere shortening.	Themoteo et al. 2022

In the context of amyloid pathology, Wilson et al. (2017) demonstrated that the administration of a subtherapeutic dose of lithium (NP03) at 0.2 mmol/kg/day for 8 weeks in McGill-R-Thy1-APP transgenic rats resulted in a significant reduction in the activity of the APP-cleaving enzyme 1 (BACE1). This decrease in BACE1 activity correlated with lower levels of early-stage amyloid pathology and improved memory function in transgenic mice. This suggests that lithium effectively targets upstream mechanisms involved in AD progression. Furthermore, the therapeutic benefits of lithium extend beyond amyloid plaques and tau-related pathology. Subsequently, Wilson et al. (2020) investigated the effects of similar doses of NP03 in the same mouse model during a 12-week trial that covered the transition phase from A β plaque-free to plaque-formation, reporting a reduced loss of cholinergic boutons in the hippocampus, lower levels of soluble and insoluble cortical A β 42, decreased hippocampal A β plaque deposition, and diminished evidence of neuroinflammation and cellular oxidative stress, all coupled with improvements in memory function.

Pereira et al. (2024) conducted a study using SAMP-8 mice, a model representative of accelerated aging, in which a similar subtherapeutic dosage of 0.2 mmol/kg/day was administered over 8 weeks. The findings revealed that lithium treatment reduced neuroinflammatory markers, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α), while simultaneously elevating levels of synaptic proteins, including synaptophysin, which indicates enhanced synaptic functionality. These results underscore lithium's potential to ameliorate neuroinflammation and promote synaptic health.

Lithium also enhances and regulates neuronal-glial interactions, which are essential for sustaining neuronal viability and synaptic health. Rocha et al. (2020) found that subtherapeutic lithium improves astrocytic and microglial functions, as well as neuronal communication. Furthermore, the effect of subtherapeutic lithium on senescence and cellular aging has been demonstrated by its capacity to preserve telomere length. Cardillo et al. (2018) reported that chronic lithium treatment (2 mmol/kg/day for 6 months) resulted in increased telomere length in the parietal cortex and hippocampus of 3xTg-AD mice, which was associated with reduced markers of cellular senescence and improved genomic stability. These studies underscore lithium's significant role as a neuroprotective agent capable of modulating critical molecular pathways, maintaining brain structure, and enhancing cognitive function. Its influence on enzymes such as GSK3 β and BACE1, along with its potential to augment neurotrophic signaling and mitigate neuroinflammation, highlights its therapeutic promise in AD. Nevertheless, further research is essential to refine

dosing strategies, evaluate long-term safety, and effectively translate these findings into clinical applications.

Cellular models

Cellular models are crucial instruments in studying the CNS. They afford comprehensive insights into the inter-cellular communication and functionality of neuronal cells. These models are especially significant in investigating neuroprotective mechanisms and neurodegenerative pathways, enhancing our understanding of the underlying biological processes.

In organotypic cultures of the hippocampus derived from SAMP-8 mice, very low doses of lithium demonstrated a crucial role in neuroprotection, with reduced neuronal loss and neuroinflammation in older individuals. These low doses also promoted a significant reduction in the CA2 area of the hippocampus and reduced the activation of NFκB and the density of inflammatory cytokines (Toricelli et al. 2021). In primary cultures of cortical and hippocampal neurons, prolonged exposure to lithium (0.02 mM, 0.2 mM, and 2 mM over 7 days) resulted in increased metabolism of membrane phospholipids, with activation of total phospholipase A2, c- and iPLA₂ (De-Paula et al., 2015). Co-cultures of cortical and hippocampal neurons with glial cells showed that chronic treatment with lithium at subtherapeutic concentrations modified the secretion of pro- and anti-inflammatory interleukins (De-Paula et al. 2016a, b). Chronic treatment with lithium at subtherapeutic doses also increased cell viability in primary cultures of cortical and hippocampal neurons. It mitigated the shortening of neuronal telomeres despite the presence of induced amyloid toxicity (Themoteo et al. 2022). Finally, De-Paula and Forlenza (2020) also investigated the effects of chronic treatment with lithium at different concentrations (including subtherapeutic doses) in primary cultures of cortical and hippocampal neurons, showing that lithium modulates the expression of several tau kinases, such as GSK3β, Akt, PKA, and CaMKII, with distinct responses between cortical and hippocampal neurons. Hippocampal neurons showed greater sensitivity to lithium at lower doses, while significant changes in cortical neurons occurred only at therapeutic doses, highlighting the regional specificity of lithium's effects. These findings underscore that lithium, even at low concentrations, can confer substantial benefits regarding neuroprotection and the prevention of neurodegeneration. That emphasizes the necessity for further investigations to elucidate its therapeutic potential and long-term safety.

Conclusion

Accumulated evidence reinforces the significant role of subtherapeutic doses of lithium in neuroprotection and the treatment of neurodegenerative conditions.

Understanding lithium's distribution within various brain structures and its influence on neurochemical and neurobiological mechanisms unveils new avenues for its therapeutic and preventive applications. Lithium pharmacokinetics demonstrate that the administered dosages and treatment duration influence both its distribution and concentration in specific brain regions and cellular models. This is critical for optimizing therapeutic efficacy while minimizing toxicity risks. In cell studies, concentrations ranged from 2 μM to 200 μM, while in animal models, doses ranged from 4 μg/kg to 10 mg/kg, administered for prolonged periods. Lithium accumulation occurs in various brain regions, including the cerebral cortex, hippocampus, and striatum, with varying concentrations according to dosage and treatment duration. At subtherapeutic doses, lithium inhibits GSK-3β, reducing tau hyperphosphorylation, amyloid plaque formation, and neuroinflammation, promoting neurogenesis, neuronal preservation, and improving memory in mice. In addition, these subtherapeutic doses activate neurotrophic pathways, such as Wnt/beta-catenin signaling, promote mitochondrial biogenesis, induce autophagy, and modulate the release of pro- and anti-inflammatory interleukins. At lower concentrations, lithium preserves telomeres, reduces oxidative stress, and improves cell viability. Thus, different doses effectively engage specific molecular targets, offering neuroprotective benefits with a lower risk of adverse effects. Cellular studies lend credence to these observations, indicating that lithium can effectively reduce neuronal loss and neuroinflammation in organotypic and primary neuron cultures. We emphasize the necessity for additional studies involving human subjects, underscoring that subtherapeutic doses of lithium offer a promising trajectory for future research.

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Author contributions

VJRP and MR equally contributed to preparation of the manuscript (literature review and manuscript writing); OVF: defined the scope and the objective of the review, and made the final revision of the text. CWLC, Jr, IRP, CCB, and COPC contributed to the literature review (credits in 'acknowledgements').

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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