Original Article

The Combined Effect of Lithium and Resistance Training on Improving Sciatic Nerve Injury by Evaluating Histological, Behavioral Changes, and Expression of Wnt/β-Catenin Pathway Genes in Rats

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ABSTRACT

Objectives: Sciatic nerve injury is a neurological disorder that leads to muscle wasting and sensory-motor dysfunction. This study aimed to investigate the effects of combined lithium and resistance training intervention on histological, behavioral and molecular indices in rats modeled with sciatic nerve injury.

Methods: In this study, 25 rats were randomly divided into five groups: sham, model (sciatic nerve injury), model + lithium (10 mg/kg, intraperitoneally for 5 days), model + resistance training (6 weeks) and model + lithium + resistance training. Interventions began 24 hours after injury. At the end of the 6-week period, the soleus muscle tissue was examined for histopathology and muscle fiber diameter. The behavioral response of the animals was assessed by hot plate test and the expression levels of Wnt and β-catenin genes in the cerebrospinal fluid were assessed by Real-time PCR.

Results: The findings showed that the model group had a significant decrease in muscle fiber diameter and a significant increase in reaction time in the hot plate test compared to the sham group. Also, the expression of Wnt and β-catenin genes in the model group increased significantly. In contrast, the treatment groups, especially the combination group (lithium + resistance training), showed a significant improvement in muscle fiber diameter, a decrease in reaction time in the behavioral test and a decrease in the expression of Wnt and β-catenin genes compared to the model group ($p<0.05$).

Conclusion: The results of this study suggest that combined lithium and resistance training therapy can improve muscle tissue structure and reduce sensory-motor disorders caused by sciatic nerve injury by reducing Wnt/β-catenin pathway activity. This combined approach can be considered as a promising therapeutic strategy for managing complications caused by peripheral nerve injuries.

Keywords: Resistance training, Lithium, Cerebrospinal fluid, Sciatic nerve injury

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Introduction

Peripheral nerve injuries, including sciatic nerve injury, are among the most challenging problems in the fields of rehabilitation medicine and neurology (1). These injuries, which are often caused by trauma, chronic stress, or surgical complications, can lead to loss of sensory-motor function, atrophy of target muscles, and ultimately a decrease in the quality of life of patients (2). In terms of physiological mechanism, sciatic nerve injury disrupts axonal integrity and neuromuscular transmission, leading to denervation of innervated muscles and subsequent atrophy through increased intracellular resting calcium levels, opening of mitochondrial transport pores, and increased production of reactive oxygen species (3). This denervation-induced muscle atrophy involves upregulation of proteolytic pathways, including the ubiquitin-proteasome systems and autophagy, which is accompanied by persistent depolarization at the neuromuscular junction, leading to sensitizing muscles to further damaging signals (3). Simultaneously, sciatic nerve injury, often associated with disc herniation or trauma, increases the concentration of structural biomarkers such as neurofilament protein, S-100, and neuron-specific enolase in the cerebrospinal fluid (4), which indicate nerve root irritation, central nervous system responses, and potential leakage of the blood–cerebrospinal fluid–cerebrospinal fluid barrier (5). Since the intrinsic capacity of peripheral nerve repair is limited, finding the effective therapeutic strategies to accelerate axonal regeneration and prevent muscle wasting, is a research priority.

The use of pharmacological agents with neuroprotective properties and physical stimuli have been considered as two complementary approaches. Lithium, an alkaline earth element, has been widely studied due to its known role in the treatment of neurological disorders (6). Studies have shown that lithium chloride administration, by inhibiting glycogen synthase kinase-3β (GSK-3β), enhances myelin and axon regeneration after sciatic nerve crush injury, thereby increasing the expression of myelin genes such as myelin protein zero (MPZ) and peripheral myelin protein 22 (PMP22), thickening myelin sheaths, and accelerating functional recovery in peripheral nerves (7). This neuroprotective effect extends to the reduction of muscle atrophy and neuropathic pain in models of sciatic nerve injury by modulating inflammatory pathways and increasing neuronal survival (8). Studies on the direct effect of lithium on cerebrospinal fluid (CSF) in sciatic nerve injury are limited, however, there are reports that lithium affects CSF biomarkers in relevant neurological contexts by increasing the levels of brain-derived neurotrophic factor (BDNF) and potentially reducing the increase in neurofilament light chain (NFL) (8).

One of the important signaling pathways that plays a dual role in the processes of nerve repair as well as in the pathology of nerve injuries is the Wnt/β-catenin pathway (9). Balanced activation of this pathway is essential for the proliferation and differentiation of neural stem cells and axonal regeneration, but its excessive and prolonged activation can hinder repair by inducing fibrosis, creating inhibitory scar gliosis, and impairing effective regeneration (10). Studies have shown that sciatic nerve injury activates the Wnt/β-catenin signaling pathway in the dorsal horn of the spinal cord, increases the expression of Wnt3a, Frizzled receptors, and nuclear translocation of β-catenin, leading to maintaining neuropathic pain by increasing neuronal excitability and activating microglia (11). This pathway, by increasing the expression of Wnt3a after nerve transection, increases proteolytic degradation and impairs regeneration, contributing to neuromuscular junction instability and muscle atrophy.

Treadmill exercise after sciatic nerve injury (SNI) has been shown to reduce mechanical allodynia by downregulating the Wnt/β-catenin signaling pathway in dorsal root ganglion (DRG) neurons during the early stages of regeneration. Specifically, exercise reduced Wnt3a expression and phosphorylated low-density lipoprotein receptor 6 (LRP6) levels at 3, 7, and 14 days after crush, while reducing β-catenin and nuclear translocation, thereby delaying the activation of a pathway that otherwise maintains neuropathic pain (12). This modulation enhances functional recovery without altering the overall timeline of nerve regeneration. The present study aims to test the hypothesis that the combination of drug treatment with lithium and physical intervention with resistance training could produce better effects through modulation of the Wnt/β-catenin pathway, leading to superior improvement in histological, behavioral, and molecular indices after sciatic nerve compression injury in an animal model.

Materials and methods

Animals

In this study, 25 male Wistar rats, 6-8 weeks old and weighing 200-180 g, were used, which were obtained from the Pasteur Institute (Tehran, Iran). The animals were kept in polycarbonate cages in a controlled environment (temperature 22-24°C, light cycle 12 hours light and 12 hours dark, humidity 55-50%) and had free access to standard food and water. All protocols were carried out in accordance with the ethical guidelines for animal research and were approved by the Ethics Committee of Karaj Azad University. The experimental schedule was as follows: Day 0: Sciatic nerve injury (or sham surgery) in all groups. Day 1: Start of interventions. Days 1-5: Lithium carbonate administration. Week 1-6: Implementation of resistance training protocol. End of week 6: Wooden beam test and cerebrospinal fluid collection. The rats were randomly assigned to five groups (n=5 in each group).

1. Sham group: Only underwent surgery to access the sciatic nerve without injury.

2. Model group: Sciatic nerve compression injury was induced.

3. Model + Lithium group: After injury, lithium carbonate (10 mg/kg, intraperitoneally) was injected daily for 5 days starting 24 hours after surgery.

4. Model + Resistance training group: After injury, resistance training protocol was started for 6 weeks starting 24 hours after surgery.

5. Model + Lithium + Resistance training group: After injury, both lithium and resistance training interventions were applied as described above.

Sciatic nerve injury

A sciatic nerve compression injury was induced under anesthesia. Briefly, the right thigh was shaved, a 2-cm incision was made, and the sciatic nerve was released. A standard compression injury was applied using silk thread, with a relatively tight knot around approximately 30–50% of the nerve diameter, 1 cm anterior to its triple bifurcation, for 30 seconds. The muscle and skin were then sutured, and the animal was caged for recovery.

Resistance training protocol

Resistance training consisted of climbing a 1.5-m vertical ladder (90° angle) with 50 steps, for 6 weeks, 5 days per week. The protocol began 24 hours after injury. The first week was considered an adaptation period: animals climbed the ladder once on the first day, three times on the second day, and eight times on the third day. From the fourth day until the end of the first week, 12 climbs were performed per session without weight bearing. From the second week, a weight equivalent to 40% of the animal's body weight was attached to its tail. This load increased by 5% each week, while the number of climbs per session remained constant at 12.

Lithium administration

Lithium carbonate (Sigma Aldrich, USA) was dissolved in 0.9% sterile saline solution. Animals in the designated groups received a daily intraperitoneal injection at a dose of 10 mg/kg for 5 consecutive days, starting 24 hours after nerve injury. This dose was selected based on previous studies that showed its neuroprotective effects in rodent models (7).

Behavioral test (Hot plate)

The hot plate test was used to assess thermal sensitivity and behavioral response to painful stimuli. This device consisted of a metal plate capable of maintaining a constant temperature of 52.5 ± 0.5 °C and a transparent glass chamber for placing the animal. Each rat was placed individually in the center of the chamber on the hot plate. Reaction time or response latency was defined as the time interval between the animal's placement on the screen and the first clear behavioral sign in response to pain (such as licking or vigorous shaking of the hind paw) and was measured with a hand-held stopwatch. To prevent tissue damage, a maximum cut-off time of 30 seconds was considered. Each animal was tested twice with a 15-minute rest interval at the end of the 6-week period and after a 10-minute familiarization period in the experimental environment, and the average of the two measurements was recorded as the final data. All animals were tested at specific times of the day and under identical environmental conditions.

Cerebrospinal fluid sampling

A combination of ketamine (100 mg/kg body weight) and xylazine (10 mg/kg) was used to anesthetize the rats. This combination was injected intraperitoneally. Then, the cerebrospinal fluid was collected from the cisterna magna area with a sterile syringe.

Evaluation of Wnt and β-catenin gene expression by Real-time PCR

The expression level of genes related to the Wnt signaling pathway (Wnt gene) and β-catenin in was evaluated using the quantitative Real-time PCR technique. First, total RNA was extracted from the cerebrospinal fluid samples using a phenol-chloroform-based RNA extraction kit (Cinagene, Iran). Then, from 1 µg of total RNA, cDNA was synthesized using a reverse transcriptase cDNA synthesis kit using a mixture of oligo (dT) and random primers. The sequences of primers specific for the target genes and the housekeeping gene (GAPDH) are shown in Table 1). Real-time PCR reactions were performed in a final volume of 20 µl and using a master mix containing the fluorescent dye SYBR Green. The reactions were performed in a Real-time PCR machine (Bio-Rad, USA) with the following program: initial denaturation step at 95°C for 5 min; then 40 cycles consisting of denaturation at 95°C for 15 s and annealing/extension at 60°C for 60 s. This was followed by a melting curve step from 65 to 95°C with 0.5° increments to confirm the specificity of the PCR products. Finally, the resulting data were analyzed by the threshold cycle (Ct) method. The relative expression level of target genes in each sample was calculated using the ΔΔCt method and normalized to the housekeeping gene GAPDH.

Statistical analysis

Statistical analysis was performed using SPSS version 24 software. One-way analysis of variance (ANOVA) was used to compare groups and Tukey's post hoc test was used for pairwise comparisons. A significance level of $p<0.05$ was considered. GraphPad Prism version 9 software was also used to draw graphs.

Results

Histological changes in the skeletal muscle tissue of the soleus are shown in Figure 1. The sham group

shows a regular and orderly tissue structure of muscle fibers without any specific disorder, in contrast to the destruction of tissue integrity in all the groups modeled with sciatic nerve injury. Lithium treatments and resistance training were able to control these injuries ($p<0.05$). The changes in the diameter of muscle fibers with Image J software was evaluated and it was found that the modeled sciatic nerve injury group had a significant decrease in the diameter of the fibers compared to the sham group. Compared to the model group, the combined treatment group (model + lithium + resistance training) showed a significant increase in muscle fiber diameter ($p<0.05$).

To investigate the behavioral response of the animals, the hot plate test was used (Figure 2). The results of one-way ANOVA showed that there was a significant difference between the different research groups in the reaction time of the hot plate test ($F=53.65$, $p<0.0001$).

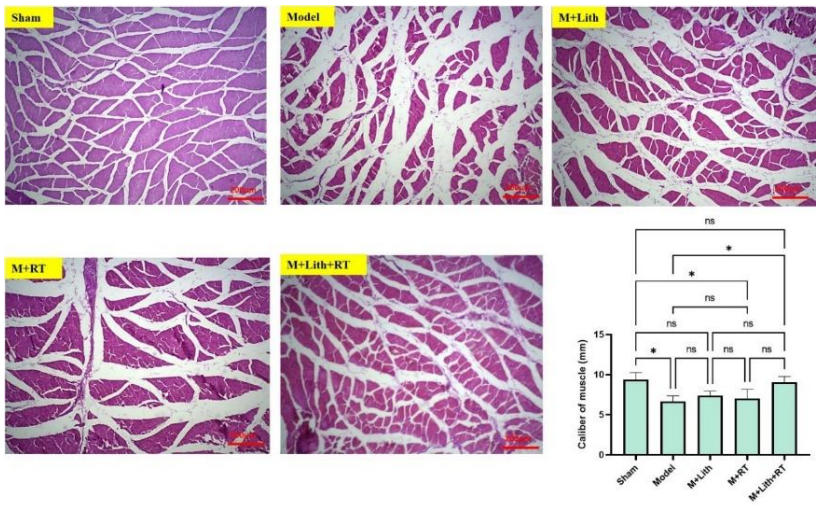


Figure 1. Histological changes of muscle tissue (using H&E staining technique) and fiber diameter in the soleus muscle of rats in different research groups, magnification 200 um. Data are shown as mean ± standard deviation (SD). Significance level: $p<0.05$ *, $p<0.01$**, $p<0.001$ ***, $p<0.0001$ **** and ns: non-significance. Abbreviations: Sham: Sham group, Model: Sciatic nerve injury group, M+Lith: Sciatic nerve injury + lithium group, M+RT: Sciatic nerve injury + resistance training group, M+Lith+RT: Sciatic nerve injury + lithium + resistance training group.

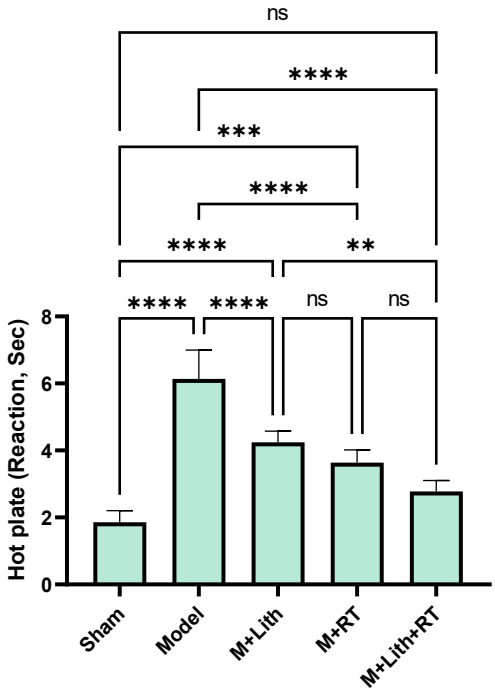


Figure 2. Reaction time of the hot plate behavioral test in rats in different research groups. Data are shown as mean ± SD. Significance level: $p<0.05$ *, $p<0.01$**, $p<0.001$ ***, $p<0.0001$ **** and ns: not significant. Abbreviations: Sham: Sham group, Model: Sciatic nerve injury group, M+Lith: Sciatic nerve injury + lithium group, M+RT: Sciatic nerve injury + resistance training group, M+Lith+RT: Sciatic nerve injury + lithium + resistance training group.

The results of Tukey's post hoc test showed that compared to the sham group, the Model ($p<0.0001$), Model+Lith ($p<0.0001$) and Model+RT ($p<0.001$) groups showed a significant increase in the reaction time in the hot plate test. However, compared to the model group, all single and combined treatment groups showed a significant decrease in the reaction time in the hot plate test, with the largest decrease being in the Model+Lith+RT group ($p<0.0001$). There was no significant difference in the retention time of the combined group compared to M+RT group, whereas combined group showed lower retention time compared to M+Lith group.

Changes in cerebrospinal fluid Wnt/βcatenin gene expression are also shown in Figure 3. There was a significant difference in the expression of Wnt ($F=8.142$, $p=0.0035$) and β-catenin ($F=26.29$, $p<0.0001$) genes in different research groups. Based on the results of Tukey's post hoc test, the expression of both Wnt and β-catenin genes increased in the nerve injury model group, while the treatment modalities, namely the Model+Lith, Model+RT, and Model+Lith+RT groups, caused a decrease in these two genes compared to the model group ($p<0.01$). We found no significant difference in the expression of these two genes in combined group in comparison with the two single groups.

Discussion

The findings of this study showed that the combined intervention of lithium and resistance training had the most effective results in improving the diameter of the soleus muscle fibers, reducing the reaction time in the thermal sensitivity test (hot plate) and reducing the expression of Wnt and β-catenin genes in the cerebrospinal fluid of the model group and even the single treatment groups, although the data were not statistically significant. These results support the initial hypothesis of the study that the combined regimen is more effective than the single treatments. The improvement in muscle fiber diameter in the combined group could be attributed to the combined effects of the two interventions. Resistance training stimulates muscle protein synthesis and prevents atrophy by increasing mechanical load and activating signaling pathways such as IGF-1/Akt (13). Lithium also inhibits GSK-3β, preventing the degradation of key cellular proteins and possibly promoting an anabolic environment (14). Corresponding studies have also shown that resistance training can delay muscle atrophy induced by nerve transection (15) and that lithium is able to preserve muscle mass in models of myopathy (16).

The results of the behavioral hot plate test, which showed improvement in thermal pain sensitivity, suggest a partial regeneration of sensory pathways or modulation of central pain processing. The reduction in reaction time in the combination group could be due to accelerated regeneration of sensory axons, reduced

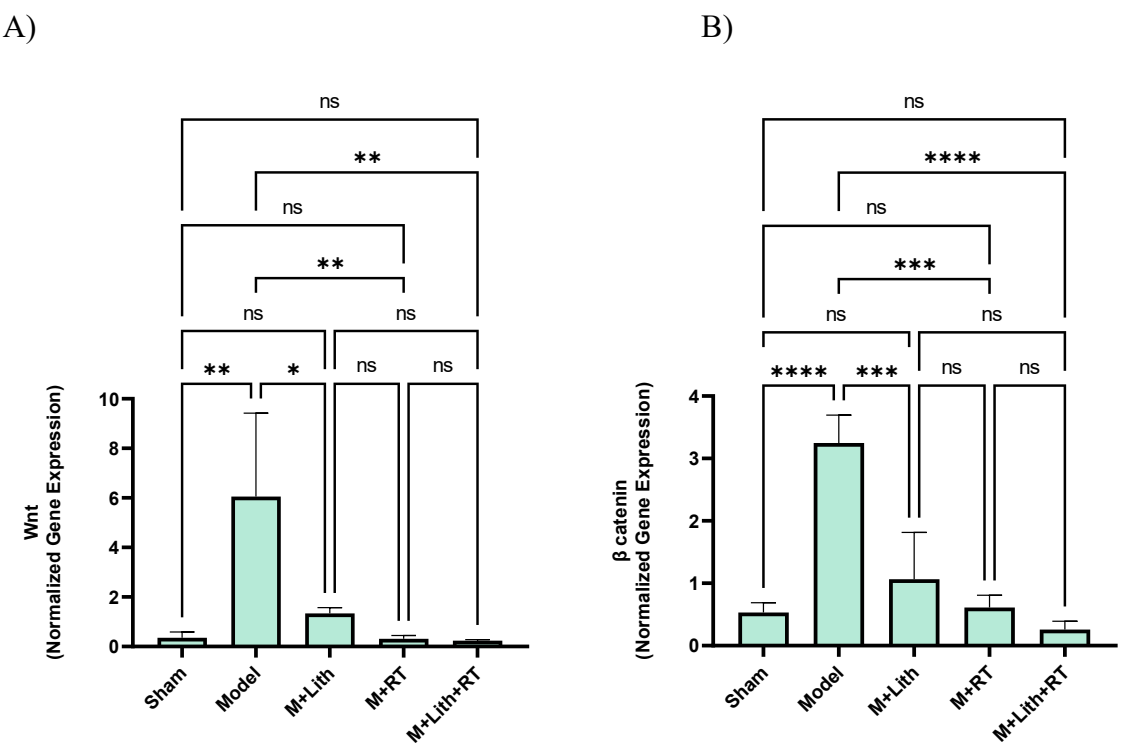


Figure 3. Expression of Wnt (a) and β -catenin (b) genes in cerebrospinal tissue in different research groups. Data are shown as mean ± SD. Significance level: $p<0.05$ *, $p<0.01$**, $p<0.001$ ***, $p<0.0001$ **** and ns: not significant. Abbreviations: Sham: Sham group, Model: Sciatic nerve injury group, M+Lith: Sciatic nerve injury + lithium group, M+RT: Sciatic nerve injury + resistance training group, M+Lith+RT: Sciatic nerve injury + lithium + resistance training group.

peripheral inflammation, or changes in neurotransmitter levels. This finding is consistent with reports that both exercise training and lithium can modulate pain threshold in models of neuropathy (17, 18). For example, a study by Zho et al. (2025) showed that exercise can alleviate neuropathic pain by increasing BDNF levels (19). On the other hand, lithium has also shown analgesic effects through GSK-3β-dependent pathways in studies such as Chuang et al. (2011) (20). However, there are some inconsistent studies (21) that challenge the sustained analgesic effects of lithium in all pain models and emphasize the dependence of the response on dose, timing, and type of injury.

A key molecular finding of this study was the increased expression of Wnt and β-catenin genes in the cerebrospinal fluid of the model group and its decrease in the treatment groups, especially the combination group. This pattern suggests a possible inappropriate activation of this pathway in response to compressive injury that may contribute to the creation of an environment that is inhibitory to repair. The dual role of the Wnt/β-catenin pathway in neural repair is well documented (22). In the early stages after injury, temporary and limited activation of this pathway is necessary to initiate repair processes, but its continued activation in other tissues is associated with complications such as fibrosis and excessive scar tissue formation (23, 24). Huang et al. (2022) showed that the inhibition of Wnt/β-catenin signaling also reduces axonal degeneration in models of parkinson's disease (25). The finding that lithium and resistance exercise reduced the expression of these genes in the present study likely indicates a favorable regulatory effect. Lithium acts as an indirect inhibitor of this pathway through inhibition of GSK-3β, as GSK-3β facilitates the phosphorylation of β-catenin and causes its degradation. On the other hand, exercise can also affect the activity of this pathway by modulating various growth factors and cytokines.

The possible mechanism of action of the combination of lithium and resistance training can be attributed to several levels. At the molecular level, lithium, by inhibiting GSK-3β (26), not only modulates the Wnt pathway, but also enhances important cell survival pathways such as the PI3K/Akt pathway and reduces apoptosis. Resistance training also exerts anabolic effects by activating the IGF-1/PI3K/Akt pathway and by increasing the secretion of neurotrophic factors such as BDNF and GDNF, creating an environment more conducive to axonal regeneration (27, 28). Thus, these two interventions likely potentiate each other's effects by enhancing common signaling networks (such as Akt) and targeting complementary aspects of pathology (such as apoptosis with lithium and atrophy with exercise). This could lead to more effective reduction of inflammation, protection of neurons and schwann cells, stimulation of axonal regeneration, and prevention of muscle wasting.

This study, despite its controlled design and valuable results, has limitations that should be considered in interpreting the findings. First, the molecular assessment focused only on the expression levels of Wnt and β-catenin genes in cerebrospinal fluid. The lack of direct measurement of the relevant proteins (via Western blot or immunohistochemistry) and the lack of assessment of the phosphorylated (activated) state of GSK-3β, which is a direct target of lithium, are important limitations. This reduces the possibility of definitive conclusions about the actual level of activity of the signaling pathway. Second, the injury model used was of an acute compressive type. While many clinical nerve injuries may be tensile, shear, or even chronic degenerative in nature, therefore, the caution is required when generalizing the results to other types of injury. Third, the resistance training protocol, although gradually progressive, only included one specific pattern (climbing a ladder). Comparison with other forms of resistance or endurance training, as well as examination of more precise parameters such as maximum muscle force production, could provide a more comprehensive picture of neuromuscular adaptations. Fourth, behavioral assessment was limited to the hot plate test. The use of complementary tests such as gait analysis (footprint), grip test, or reflex assessment could have covered the motor and sensory dimensions of recovery more completely. Fifth, the study period was 6 weeks, and the long-term effects of this combination treatment as well as the sustainability of the observed improvements remain uncertain. Finally, given the nature of the animal study, the direct translation of these findings to the human population requires clinical trial studies, taking into account the possible side effects of lithium and the establishment of safe and personalized exercise protocols for patients.

Conclusions

Based on the findings of this study, it can be concluded that the combined intervention of lithium and resistance training, compared to the single application of each, produces superior healing effects on sciatic nerve injury in a rat model, although these effects were not statistically significant. This healing was observed at both the tissue level (prevention of atrophy of soleus muscle fibers), at the functional level (reduction of reaction time in the thermal pain test), and at the molecular level (reduction of Wnt and β-catenin gene expression in cerebrospinal fluid). This pattern of results reinforces the hypothesis that the aforementioned combination therapy may act by modulating the activity of the Wnt/β-catenin signaling pathway. Therefore, this combined approach can be considered as a complementary and promising therapeutic strategy for the management of complications resulting from peripheral nerve injuries. However, final confirmation of the precise mechanisms of the action and determination of optimal therapeutic

parameters (dose, timing, and type of exercise) to achieve maximum efficacy and safety require further studies focusing on proteomic assessments, long-term follow-up, and ultimately controlled clinical trials.

Conflict of Interest

The authors declared that they have no conflict of interest.

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