Research Article

Combined lithium and resistance training exerts a synergistic effect on functional recovery and attenuates neuroinflammation in a rat model of sciatic nerve injury

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Abstract

Sciatic nerve injury results in significant functional impairment and is associated with neuroinflammatory responses. While lithium and exercise have shown independent neuroprotective potential, their combined effects remain less explored. This study investigated the therapeutic efficacy of lithium, resistance training, and their combination on functional recovery and neuroinflammatory markers in a rat model of sciatic nerve injury. Twenty-five rats were randomly divided into five groups: Sham, Model (sciatic nerve injury), Model+Lithium (M+Lith), Model+Resistance training (M+RT), and Model+Lithium+Resistance training (M+Lith+RT). Lithium carbonate (10 mg/kg, i.p.) was administered for 5 days, and resistance training was conducted for 6 weeks, with both interventions starting 24 hours' post-injury. Functional recovery was assessed using the beam walk test. Neuroinflammation was evaluated by measuring the activity of myeloperoxidase (MPO) and nitric oxide (NO) in the cerebrospinal fluid at the end of the 6-week intervention period. Sciatic nerve injury (Model group) induced a significant deficit in beam test performance compared to the Sham group ($p<0.001$). All treatment groups (Lithium, Resistance training, and Combined) showed significant improvement in functional scores compared to the Model group, with the Combined treatment group showing significantly greater recovery than either monotherapy ($p<0.05$). Furthermore, the Model group exhibited a significant increase in MPO and NO levels. Resistance training alone and in combination with lithium significantly attenuated this increase ($p< 0.0001$). Interestingly, lithium monotherapy did not reduce the elevated neuroinflammatory markers. Our findings demonstrate that resistance training alone effectively reduces neuroinflammation and improves functional recovery after sciatic nerve injury. The combination of lithium and resistance training yields a synergistic effect, resulting in the most significant functional improvement, suggesting a promising combined therapeutic strategy for peripheral nerve injury.

Key Words: Apoptosis, Sciatic nerve injury, Neuroinflammation, Lithium, Resistance training, Myeloperoxidase, Nitric oxide

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Introduction

Peripheral nerve injuries (PNIs), particularly those involving the sciatic nerve, represent a significant clinical challenge in neurology and rehabilitation medicine, often leading to long-term sensorimotor deficits, neuropathic pain, and a substantial reduction in quality of life (Navarro et al., 2007). The initial mechanical trauma triggers a complex and sustained secondary injury cascade, characterized by robust neuroinflammatory responses that exacerbate tissue damage and hinder axonal regeneration (Theus, 2024). This inflammatory milieu is a critical determinant of the functional outcomes following nerve injury. Despite advances in microsurgical techniques, functional recovery is frequently suboptimal, necessitating the development of effective adjuvant pharmacological and rehabilitative strategies to modulate the post-injury environment and improve regenerative potential (Chen et al., 2007).

A hallmark of the secondary injury phase is the activation of central glial cells (e.g., spinal microglia) and the infiltration of immune cells, leading to the production of a barrage of pro-inflammatory mediators (Patel et al., 2025). Among these, myeloperoxidase (MPO) and nitric oxide (NO) have been implicated as key contributors to oxidative stress and subsequent neuronal damage (Chen et al., 2020; Wei et al., 2000). MPO, derived from infiltrating neutrophils, generates hypochlorous acid and other reactive oxidants, while excessive NO, produced by inducible nitric oxide synthase (iNOS), can form peroxynitrite, leading to lipid peroxidation and protein nitration (Schwartz & Yoles, 2006). The dysregulated activity of these molecules within the central nervous system environment, accessible via the cerebrospinal fluid, creates an inhibitory milieu for repair, making them critical targets for therapeutic intervention (Xiong et al., 2018).

In the search for effective treatments, lithium carbonate has re-emerged as a potential neuroprotective agent. Beyond its well-established role in psychiatry, lithium has been shown to promote neuronal survival and synaptic plasticity through the in-

-hibition of glycogen synthase kinase-3β (GSK-3β) and the upregulation of brain-derived neurotrophic factor (BDNF) (Chiu & Cline, 2010). Concurrently, physical rehabilitation, particularly resistance training, is a cornerstone of functional recovery. Resistance exercise has been demonstrated to reduce inflammation, enhance neurotrophic support, and improve motor function in various neurological disorder models (Stone et al., 2023). However, the specific impact of resistance training on MPO and NO dynamics following sciatic injury remains underexplored. Furthermore, while lithium and exercise have been investigated independently, their potential synergistic effects in a combinatory treatment paradigm for PNI are not well-defined, presenting a significant gap in the current literature.

Therefore, the present study was designed to investigate the therapeutic potential of lithium monotherapy, resistance training, and their combination in a rat model of sciatic nerve injury. We hypothesized that both interventions would confer beneficial effects, but that their combination would produce a synergistic enhancement of functional recovery. To test this, we evaluated motor coordination and balance using the beam walk test and quantified the extent of neuroinflammation by measuring MPO and NO activity in the cerebrospinal fluid. Our findings aim to provide a scientific basis for a novel, combined therapeutic strategy to ameliorate the detrimental consequences of peripheral nerve injury.

Materials and methods

Animals

In this study, 25 male Wistar rats, 6-8 weeks old, weighing 180-200 grams, were obtained from the Pasteur Institute. Rats were housed in polycarbonate cages in a controlled environment (temperature 22-24°C, 12-hour light-dark cycle, humidity of 50-55%) with ad libitum access to food and water. All procedures were approved by the university ethics committee and complied with institutional guidelines for animal care. The experimental timeline was as follows: Day 0: Sciatic nerve injury surgery (or sham surgery) was performed on all groups. Day 1: Interventions began. Day 1-5: Lithium carbonate administration. Day 1-6 weeks: Resistance training protocol. End of Week 6: Final beam walk test and cerebrospinal fluid collection. Rats were randomly assigned to one of five groups (n=5 per group):

1. Sham group: Underwent surgical exposure of the sciatic nerve without injury.

2. Model group: Underwent sciatic nerve crush injury.

3. Model + Lithium group (M+Lith): Received sciatic nerve injury and was administered lithium carbonate (10 mg/kg, intraperitoneally) once daily for 5 days, starting 24 hours post-surgery.

4. Model+Resistance training group (M+RT): Received sciatic nerve injury and underwent the 6-week resistance training protocol, starting 24 hours' post-surgery.

5.Model+Lithium+Resistance training group (M+Lith+RT): Received sciatic nerve injury and received both the lithium and resistance training interventions as described above.

Induction of the sciatic nerve injury model

The sciatic nerve crush injury was induced under anesthesia. Briefly, the right thigh was shaved, a 2-cm incision was made, and the sciatic nerve was exposed. A standardized crush injury was performed by applying a relatively tight knot around approximately 30-50% of the nerve diameter, 1 cm proximal to its trifurcation, for 30 seconds using a 6-0 silk suture. The muscle and skin were then sutured, and the animal was allowed to recover.

Resistance training protocol

Resistance training consisted of climbing a 1.5-meter vertical ladder (90º) with 50 rungs, 5 days per week for 6 weeks. The protocol began 24 hours' post-injury. The first week was an adaptation period: animals climbed the ladder once on day 1, three times on day 2, and eight times on day 3. From day 4 to the end of week 1, they performed 12 climbs per session without weight. From week 2, a weight corresponding to 40% of the rat's body weight was attached to the tail. This load was increased by 5% each subsequent week, while the number of climbs remained constant at 12 per session.

Lithium Administration

Lithium carbonate (Sigma-Aldrich, St. Louis, MO, USA) was dissolved in sterile 0.9% saline. Animals in the designated groups received a daily intraperitoneal injection of 10 mg/kg for 5 consecutive days, commencing 24 hours after nerve injury. The dose was selected based on previous studies demonstrating neuroprotective efficacy in rodent models of neural injury without significant side effects (Jafari et al., 2018).

Beam test

Motor coordination and balance were assessed using the beam walk test on a narrow, elevated beam (specify dimensions, e.g., 100 cm long, 2.5 cm wide). The test was performed pre-injury (baseline) and at the end of the 6-week intervention period. Rats were required to traverse the beam. A foot slip was defined as any instance where a paw slipped off the top surface of the beam. The functional score was defined as the total number of foot slips made during the traverse, with a higher score indicating greater motor impairment.

Cerebrospinal fluid sampling

Ketamine (100 mg/kg body weight) plus xylazine (10 mg/kg) were used to anesthetize male Wistar rats. This combination was injected intraperitoneally into the rats. The reason for choosing intraperitoneal injection was the rapid absorption of the injected substances and their entry into the animal's circulatory system. Then, cerebrospinal fluid was drawn from the cisterna magna area with a syringe.

Biochemical assays

Concentrations of neuroinflammatory markers, myeloperoxidase (MPO) and nitric oxide (NO), were measured in the cerebrospinal fluid. MPO levels were quantified using a commercial ELISA kit (Navand Lab kit, Iran, Version 0.85), and NO metabolites (nitrate/nitrite) were measured using a colorimetric assay kit (Navand Lab kit, Iran, Version 0.85), according to the manufacturers' instructions. For the NO assay, 10 µl of the sample was mixed with 80 µl of diluted Griess Reagent R1 and incubated for 10 minutes at room temperature and away from light. Then, 110 µl of Griess Reagent R2 was added to the mixture. The plate was read with a microplate reader at a wavelength of 650 nm (630 to 650 nm) at 1 and 10 minutes, and quantitative values were obtained.

Statistical analysis

Statistical analysis was performed using SPSS v24. One-way analysis of variance was used to compare groups. Tukey's post hoc test was also used to compare between groups. The significance level was considered $p<0.05$. GraphPad Prism 9 software was also used to draw graphs.

Results

Beam test

The results of the beam test score are shown in Figure 1. According to the results of the one-way ANOVA test, there was a significant difference in the BEAM test score between the different research groups ($F = 44.33$, $p<0.0001$). The results of the Tukey post hoc test showed that compared to the Sham group, all the sciatic nerve injury groups (Model, Model+Lithium, Model+Resistance training, Model+Lithium+Resistance training groups) showed a significant decrease in the behavioral fear test score ($p<0.001$). Compared to the Model group (sciatica injury), the Model+Lithium, Model+Resistance training, and Model+Lithium+Resistance training groups showed an increase in the BEAM test score, with the highest increase being related to the combined exercise and lithium treatment group ($p<0.05$).

Myeloperoxidase enzyme

Changes in cerebrospinal fluid Myeloperoxidase enzyme activity

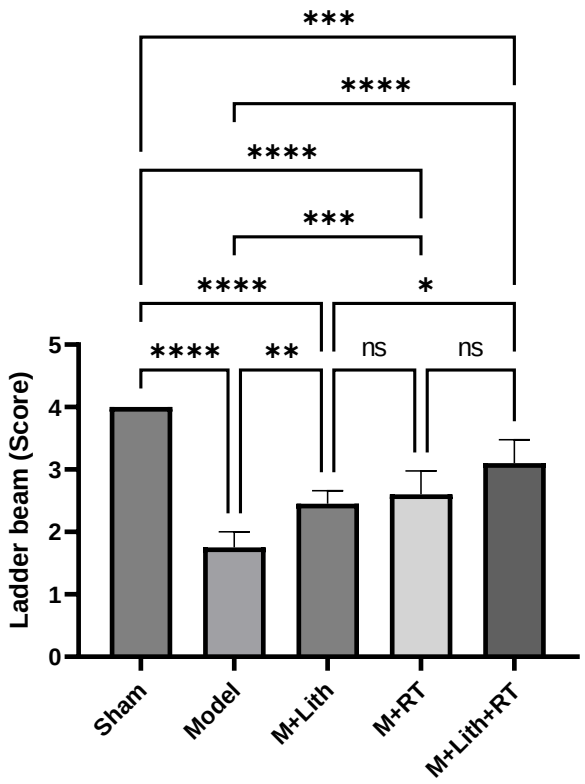

Figure 1. Behavioral test scores of ladder beam in rats at different research groups. Data are shown as means ± standard deviation (SD). p Value: $p<0.05$ *, $p<0.01$**, $p<0.001$ ***, $p<0.0001$ ****. Abbreviations: M: Model, Lith: Lithium, RT: Resistance Training.

are shown in Figure 2. According to the results of one-way ANOVA, there is a significant difference in the activity of Myeloperoxidase enzyme between the different research groups ($F=39.06$, $p<0.0001$). The results of Tukey's post hoc test showed that compared to the Sham group, the Model (sciatic nerve injury) and Model + Lithium groups showed a significant increase in the activity of Myeloperoxidase enzyme in cerebrospinal fluid ($p< 0.001$). In contrast, compared to the Model (sciatic nerve injury) and Model + Lithium groups, the Model+ Resistance training and Model + Lithium+Resistance training groups showed a significant decrease in the activity of Myeloperoxidase enzyme in cerebrospinal fluid ($p<0.0001$).

Nitric oxide

Changes in nitric oxide activity in cerebrospinal fluid are shown in Figure 3. According to the results of one-way ANOVA, there was a significant difference in nitric oxide activity between the different research groups ($F=181.4$, $p<0.0001$). The results of Tukey's post hoc test showed that compared to the Sham group, the Model (sciatic nerve injury) and Model+Lithium groups showed a significant increase in nitric oxide in cerebrospinal fluid ($p<0.001$). In contrast, compared to the Model (sciatic nerve injury) and the

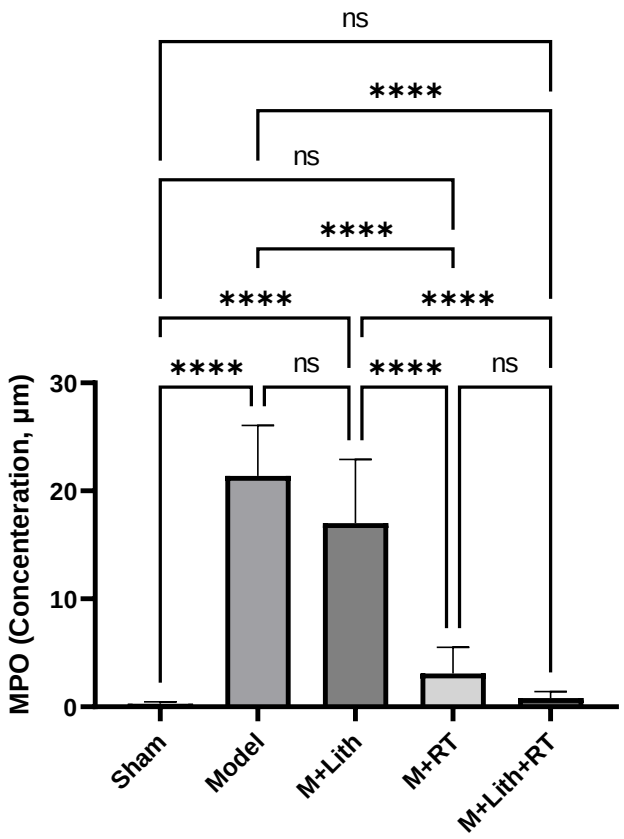

Figure 2. Measuring myeloperoxidase (MPO) enzyme activity in cerebrospinal fluid of rats from different research groups. Data are shown as means ± standard deviation (SD). p Value: p<0.05 *, p<0.01 **, p<0.001 ***, p<0.0001 ****. Abbreviations: M: Model, Lith: Lithium, RT: Resistance Training.

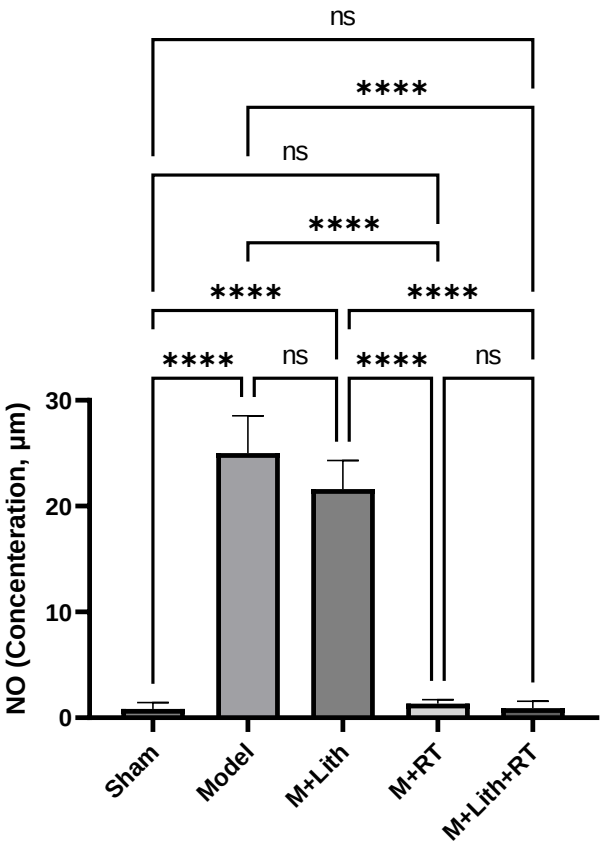

Figure 3. Measuring nitric oxide (NO) activity in cerebrospinal fluid of rats from different research groups. Data are shown as means ± standard deviation (SD). p Value: p<0.05 *, p<0.01**, p<0.001 ***, p<0.0001 ****. Abbreviations: M: Model, Lith: Lithium, RT: Resistance Training.

Model+Lithium groups, the Model+Resistance training and Model+Lithium+Resistance training groups showed a significant decrease in nitric oxide in cerebrospinal fluid (p<0.0001).

Discussion

The principal finding of this study is that the combination of lithium and resistance training confers a synergistic enhancement of functional recovery following sciatic nerve injury in a rat model, surpassing the effects of either intervention alone. Furthermore, our results illuminate a critical divergence in the mechanisms of action for these two therapies: resistance training potently attenuates key markers of neuroinflammation (MPO and NO), whereas lithium monotherapy, while improving functional outcomes, does not significantly impact these specific inflammatory parameters. This suggests that the synergistic benefit arises from the convergence of complementary, rather than overlapping, neuroprotective and neurorestorative pathways.

The initial phase of peripheral nerve injury is characterized by a robust neuroinflammatory response, a double-edged sword that clears debris but can also exacerbate secondary damage and im-pede regeneration (Chen et al., 2016). Our data confirm that sciatic nerve crush injury induces a significant state of neuroinflammation, as evidenced by elevated levels of MPO and NO in the cerebrospinal fluid. MPO, a hallmark enzyme of neutrophil infiltration, produces hypochlorous acid and other reactive oxygen species that contribute to oxidative stress, lipid peroxidation, and direct damage to neurons and glia (Del Moro et al., 2025). Concurrently, the surge in NO, primarily from activated microglia and infiltrating macrophages via inducible nitric oxide synthase (iNOS), can lead to the formation of peroxynitrite, a potent oxidant that nitrates proteins and damages DNA, ultimately promoting neuronal apoptosis (Choi, 1993). The significant reduction of both MPO and NO in the resistance training groups (both alone and combined) indicates a powerful anti-inflammatory effect of this rehabilitative modality.

The cellular mechanisms through which resistance training mitigates neuroinflammation are multifaceted. Exercise is a well-established inducer of brain-derived neurotrophic factor (BDNF), which not only supports neuronal survival and synaptic plasticity but also exerts potent anti-inflammatory effects. BDNF can suppress the activation of the NLRP3 inflammasome in microglia,

a key signaling complex that drives the production of pro-inflammatory cytokines like IL-1β and IL-18 (Jin et al., 2021).

Furthermore, muscle contraction during resistance exercise releases myokines, such as irisin and IL-6, into the circulation. Irisin has been shown to cross the blood-brain barrier and promote a shift in microglial polarization from the pro-inflammatory M1 phenotype (which produces iNOS and TNF-α) towards the anti-inflammatory, regenerative M2 phenotype (Zhang et al., 2025). This phenotypic switch would directly explain the observed reduction in NO production. The reduction in MPO likely reflects decreased neutrophil chemotaxis and infiltration, potentially mediated by exercise-induced modulation of adhesion molecules and chemokines like ICAM-1 and CXCL1 (Darkwah et al., 2021).

In stark contrast, lithium monotherapy failed to attenuate the elevated levels of MPO and NO, despite improving functional recovery in the beam walk test. This dissociation underscores that lithium's primary benefit in this model is not mediated through the suppression of these particular acute inflammatory oxidants. This finding aligns with literature indicating that lithium's neuroprotective properties at certain doses and durations are primarily mediated through direct effects on neuronal resilience rather than broad anti-inflammatory actions. Instead, lithium's well-characterized mechanism revolves around the inhibition of glycogen synthase kinase-3β (GSK-3β). GSK-3β is a constitutively active serine/threonine kinase that acts as a central node in numerous pathways detrimental to neuronal survival and axonal regeneration. Its inhibition by lithium leads to the stabilization of β-catenin, promoting transcriptional programs for cell survival and synaptogenesis (Kaidanovich-Beilin & Woodgett, 2011) are critically in the context of nerve regeneration, GSK-3β inhibition activates the mTOR pathway and enhances the expression of growth-associated proteins like GAP-43, thereby stimulating axonal elongation and remyelination (Zhou & Snider, 2005). Therefore, lithium's functional benefit likely stems from its direct pro-regenerative and pro-survival signaling within neurons, effectively "priming" them for recovery independent of a broad anti-oxidant effect.

The observed synergy in the combined treatment group can thus be rationally explained by this mechanistic dichotomy. Resistance training creates a permissive CNS environment by quelling the hostile neuroinflammatory milieu (reducing MPO/NO), thereby removing barriers to regeneration. Simultaneously, lithium directly stimulates the intrinsic growth machinery of the injured neuron via GSK-3β inhibition. The convergence of these two pathways-an external, inflammation-modulating signal from exercise and an internal, growth-promoting signal from lithium-would be expected to produce a more robust and accelerate the functional recovery than either could achieve alone. This is analogous to clearing a path (resistance training) while simultaneously providing a more powerful engine for the vehicle (lithium).

Several limitations of this study should be acknowledged. First, we measured neuroinflammatory markers in the cerebrospinal fluid, which provides a global picture of CNS inflammation but may not fully reflect the precise molecular changes at the site of peripheral nerve injury (the sciatic nerve or the corresponding dorsal root ganglia). Future studies should include tissue-specific analysis. Second, the lithium dosing regimen (10 mg/kg for 5 days) was relatively short-term; a longer course of treatment might reveal effects on later phases of inflammation or different inflammatory mediators. Finally, while we have inferred cellular mechanisms based on established literature, direct evidence of microglial polarization, BDNF levels, and GSK-3β activity in our model would strengthen the proposed mechanistic framework.

Conclusion

In conclusion, our findings demonstrate a clear therapeutic synergy between lithium and resistance training for functional recovery after sciatic nerve injury. We propose a model where these interventions act through distinct yet complementary cellular pathways: resistance training primarily attenuates neuroinflammation by modulating glial activity and immune cell infiltration, while lithium directly promotes neuronal resilience and axonal regeneration via intracellular kinase inhibition. This combination strategy, targeting both the extrinsic inhibitory environment and the intrinsic regenerative capacity of the neuron, presents a promising and rational translational approach for the treatment of peripheral nerve injuries. Future research should focus on optimizing the timing and dosage of this combined regimen and elucidating the precise molecular crosstalk between exercise-induced myokines and lithium-sensitive signaling cascades.

What is already known on this subject?

Peripheral nerve injuries (PNIs), particularly those involving the sciatic nerve, represent a significant clinical challenge in neurology and rehabilitation medicine, often leading to long-term sensorimotor deficits, neuropathic pain, and a substantial reduction in quality of life.

What this study adds?

The combination strategy (resistance training while lithium), targeting both the extrinsic inhibitory environment and the intrinsic regenerative capacity of the neuron, presents a promising and rational translational approach for the treatment of peripheral nerve injuries.

Organ Cross-Talk Tips:

- Neuroinflammation from a peripheral nerve injury was detected by analyzing biomarkers (MPO and NO) in the cerebrospinal fluid, showing communication between the peripheral nervous system and the central nervous system.
- The combination of lithium (a systemic drug) and resistance training (physical activity) produced a greater functional recovery than either alone, suggesting their cross-talk mechanisms work on different but complementary pathways.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest in the present research.

Ethical approval All procedures were approved by the university ethics committee and complied with institutional guidelines for animal care.

Informed consent Animal study.

Author contributions

Conceptualization: S.S., F.F, A.S., A.R., Methodology: S.S., F.F, A.S., A.R., Software: S.S., F.F, A.S., A.R., Validation: S.S., F.F, A.S., A.R.,; Formal analysis: S.S., F.F, A.S., A.R.,; Investigation: S.S., F.F, A.S., A.R.,; Resources: S.S., F.F, A.S., A.R.,; Data curation: S.S., F.F, A.S., A.R.,; Writing - original draft: S.S., F.F, A.S., A.R.,; Writing–review & editing S.S., F.F, A.S., A.R.,; Visualization: S.Sh., H.A, F.Gh., M.GH.,; Supervision: F.F.; Project administration: S.S.,.; Funding acquisition: S.S.

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