

LITIJUM KAO NEUROREGENERATIVNI MODULATOR U REPARACIJI PERIFERNIH NERAVA: MEHANISTIČKI UVIDI I STRATEGIJE BIOINŽENJERSKE ISPORUKE – SISTEMATSKI PREGLED

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REVIEW ARTICLE

LITHIUM AS A NEUROREGENERATIVE MODULATOR IN PERIPHERAL NERVE REPAIR: MECHANISTIC INSIGHTS AND BIOENGINEERED DELIVERY STRATEGIES – A SYSTEMATIC REVIEW

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SAŽETAK

Uvod: Povrede perifernih nerava (PNI) predstavljaju značajan klinički problem, sa ograničenim funkcionalnim oporavkom uprkos napretku mikrohkirurških tehnika. Litijum se poslednjih godina ispituje kao neuroaktivni agens sa efektima na preživljavanje neurona, funkciju Švanovih ćelija, regeneraciju aksona i remijelinizaciju. Ovaj pregled analizira dokaze o ulozi litijuma u regeneraciji perifernih nerava, sa fokusom na bioinženjerske strategije isporuke.

Metode: Sproveden je sistematski pregled literature prema PRISMA smernicama u bazama PubMed, Scopus i Web of Science, zaključno sa aprilom 2026. godine. Uključene su studije koje se bave litijumom u regeneraciji perifernih nerava, biologijom Švanovih ćelija, neuroprotektivnim efektima, remijelinizacijom i biomaterijalima za lokalnu isporuku. Podaci su kvalitativno analizirani sa fokusom na eksperimentalne modele i translacioni značaj.

Rezultati: Pretkliničke studije ukazuju na to da litijum može pospešiti regeneraciju perifernih nerava putem modulacije signalizacije glikogen-sintaza-kinaze-3β (GSK-3β), aktivacije pro-survival puteva, indukcije autofagije i regulacije proliferacije i mijelinizacije Švanovih ćelija. Većina dokaza potiče iz in vitro i životinjskih modela, sa poboljšanom regeneracijom aksona, remijelinizacijom i funkcionalnim oporavkom. Deo podataka potiče iz studija centralnog nervnog sistema i tumačen je oprezno zbog razlika u regenerativnom kapacitetu CNS i PNS. Novija istraživanja ukazuju na to da biomaterijali sa litijumom, uključujući hidrogelne, nervne konduite, adhezivne polimere i nanostrukturirane sisteme, mogu omogućiti lokalnu i produženu isporuku uz smanjenje sistemske toksičnosti.

Zaključak: Litijum predstavlja obećavajući dodatni neuroregenerativni modulator u modelima povrede perifernih nerava, naročito kada se primenjuje kroz lokalne bioinženjerske sisteme. Dokazi su i dalje pretežno pretklinički, a translacija je ograničena uskim terapijskim prozorom i sistemskom toksičnošću. Potrebne su dalje translacione i kliničke studije radi procene bezbednosti i terapijskog potencijala.

Cljučne reči: litijum, periferni nervi, bioinženjering, GSK-3β, neuroregeneracija

ABSTRACT

Introduction: Peripheral nerve injuries (PNIs) remain a major clinical challenge with limited functional recovery despite advances in microsurgery. Lithium has emerged as a neuroactive agent with effects on neuronal survival, Schwann cell function, axonal regeneration, and remyelination. This review evaluates evidence on lithium in peripheral nerve regeneration, focusing on bioengineered delivery approaches.

Methods: A PRISMA-guided systematic review was performed using PubMed, Scopus, and Web of Science up to April 2026. Studies addressing lithium in peripheral nerve regeneration, Schwann cell biology, neuroprotection, remyelination, and biomaterial-based delivery systems were included. Data were synthesized qualitatively with emphasis on experimental and translational findings.

Results: Preclinical studies suggest lithium enhances peripheral nerve regeneration via modulation of glycogen synthase kinase-3β (GSK-3β), activation of pro-survival pathways, autophagy induction, and effects on Schwann cell proliferation and myelination. Most evidence comes from in vitro and animal models, showing improved axonal regrowth, remyelination, and functional recovery. Some supporting data derive from central nervous system models and were interpreted with caution due to inherent differences in regenerative capacity between the central and peripheral nervous systems. Newer studies indicate that lithium-loaded biomaterials, including hydrogels, nerve conduits, adhesive polymers, and nanostructured systems, may enable localized delivery with reduced systemic toxicity.

Conclusions: Lithium appears to be a promising adjunct in peripheral nerve repair, especially when delivered through bioengineered local systems. However, current evidence is largely preclinical, and translation is limited by a narrow therapeutic window and systemic toxicity. Further studies are needed to clarify safety and clinical applicability.

Keywords: lithium, peripheral nerves, bioengineering, GSK-3β, neuroregeneration

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UVOD

Povrede perifernih nerava (PNI) predstavljaju čest i klinički značajan problem u neurohirurgiji, ortopediji i traumatologiji, sa posledičnim motornim i senzitivnim deficitima koji često dovode do dugotrajne invalidnosti i smanjenja kvaliteta života pacijenata [1]. Uprkos napretku mikrohirurških tehnika rekonstrukcije nerva, uključujući direktne anastomoze, autologne nervne graftove i primenu nervnih konduita, funkcionalni oporavak ostaje nepredvidiv, naročito kod lezija sa većim defektom nervnog tkiva ili odloženom hirurškom intervencijom [2,3]. Glavno ograničenje savremenih terapijskih pristupa nije samo tehnička rekonstrukcija kontinuiteta nerva, već inherentno spor i često nepotpun biološki proces regeneracije aksona i reinervacije ciljnih struktura [4].

Nakon povrede perifernog nerva dolazi do Valerove degeneracije distalnog segmenta aksona, što uključuje fragmentaciju aksona i mijelina, kao i aktivaciju lokalnog imunološkog odgovora sa infiltracijom makrofaga koji učestvuju u čišćenju celularnog detritusa [5]. Paralelno sa ovim procesom, Švanove ćelije prolaze kroz značajno fenotipsko reprogramiranje i prelaze u tzv. stanje „popravke“, koje je ključno za uspešnu regeneraciju nerva. U ovom fenotipu, one gube mijelinizujuća svojstva i dobijaju regenerativni profil karakterisan povećanom proliferacijom, migracijom i ekspresijom neurotrofičnih faktora koji usmeravaju aksonski rast [6]. Takođe formiraju tzv. Bungnerove trake koje služe kao vodiči za regenerišuće aksone ka distalnim ciljnim strukturama, čime obezbeđuju prostornu i biohemijsku podršku procesu regeneracije [5]. Međutim, ovaj reparativni program je vremenski ograničen, a produžena denervacija dovodi do progresivnog gubitka fenotipske stabilnosti Švanovih ćelija, smanjenja njihove podrške aksonskom rastu i značajnog pada regenerativnog kapaciteta nerva [4].

METODOLOGIJA

Pretragom literature u bazama PubMed, Scopus i Web of Science identifikovano je ukupno 196 zapisa relevantnih za temu litijuma i regeneracije perifernih nerava. Nakon uklanjanja duplikata, za početni skrining ostalo je 158 publikacija.

Tokom faze skrininga izvršena je procena naslova i apstrakata svih identifikovanih radova. Isključena su 104 rada zbog nedovoljne povezanosti sa regeneracijom perifernih nerava, odsustva podataka o litijumu ili nedostatka eksperimentalne, translacione ili mehaničke relevantnosti za temu ovog pregleda.

Potpuna analiza teksta sprovedena je za 54 publikacije. Tokom procene podobnosti dodatno je isključeno 28 radova zbog preklapanja podataka, nedostatka originalnih nalaza, odsustva jasne veze sa perifernim

INTRODUCTION

Peripheral nerve injuries (PNIs) are a frequent and clinically significant problem in neurosurgery, orthopedics, and traumatology, often resulting in motor and sensory deficits that can lead to long-term disability and a reduction in patients' quality of life [1]. Despite advances in microsurgical nerve reconstruction techniques, including direct anastomosis, autologous nerve grafting, and the use of nerve conduits, functional recovery remains unpredictable, particularly in cases involving extensive nerve tissue defects or delayed surgical intervention [2,3]. The main limitation of current therapeutic approaches lies not only in the technical restoration of nerve continuity but also in the inherently slow and often incomplete biological processes of axonal regeneration and reinnervation of target structures [4].

Following peripheral nerve injury, Wallerian degeneration occurs in the distal axonal segment and is characterized by fragmentation of the axon and myelin, accompanied by activation of the local immune response and infiltration of macrophages, which contribute to the clearance of cellular debris [5]. In parallel, Schwann cells undergo significant phenotypic reprogramming and transition into a so-called "repair" state, which plays a crucial role in successful nerve regeneration. In this phenotype, they lose their myelinating properties and acquire a regenerative profile characterized by enhanced proliferation and migration, as well as increased expression of neurotrophic factors that support and guide axonal growth [6]. They also form the so-called Bands of Büngner, which serve as guiding structures for regenerating axons toward distal target tissues, providing essential spatial and biochemical support throughout the regeneration process [5]. However, this reparative program is time-limited, and prolonged denervation leads to progressive loss of Schwann cell phenotypic stability, reduced support for axonal growth, and a substantial decline in the nerve's regenerative capacity [4].

METHODOLOGY

A literature search of the PubMed, Scopus, and Web of Science databases identified 196 records relevant to lithium and peripheral nerve regeneration. Following the removal of duplicate records, 158 publications remained for initial screening.

During the screening phase, the titles and abstracts of all identified publications were evaluated. A total of 104 papers were excluded due to insufficient relevance to peripheral nerve regeneration, the absence of data on lithium, or a lack of experimental, translational, or mechanistic relevance to the scope of this review.

nervnim sistemom ili ograničene relevantnosti za regenerativne procese nakon povrede nerva.

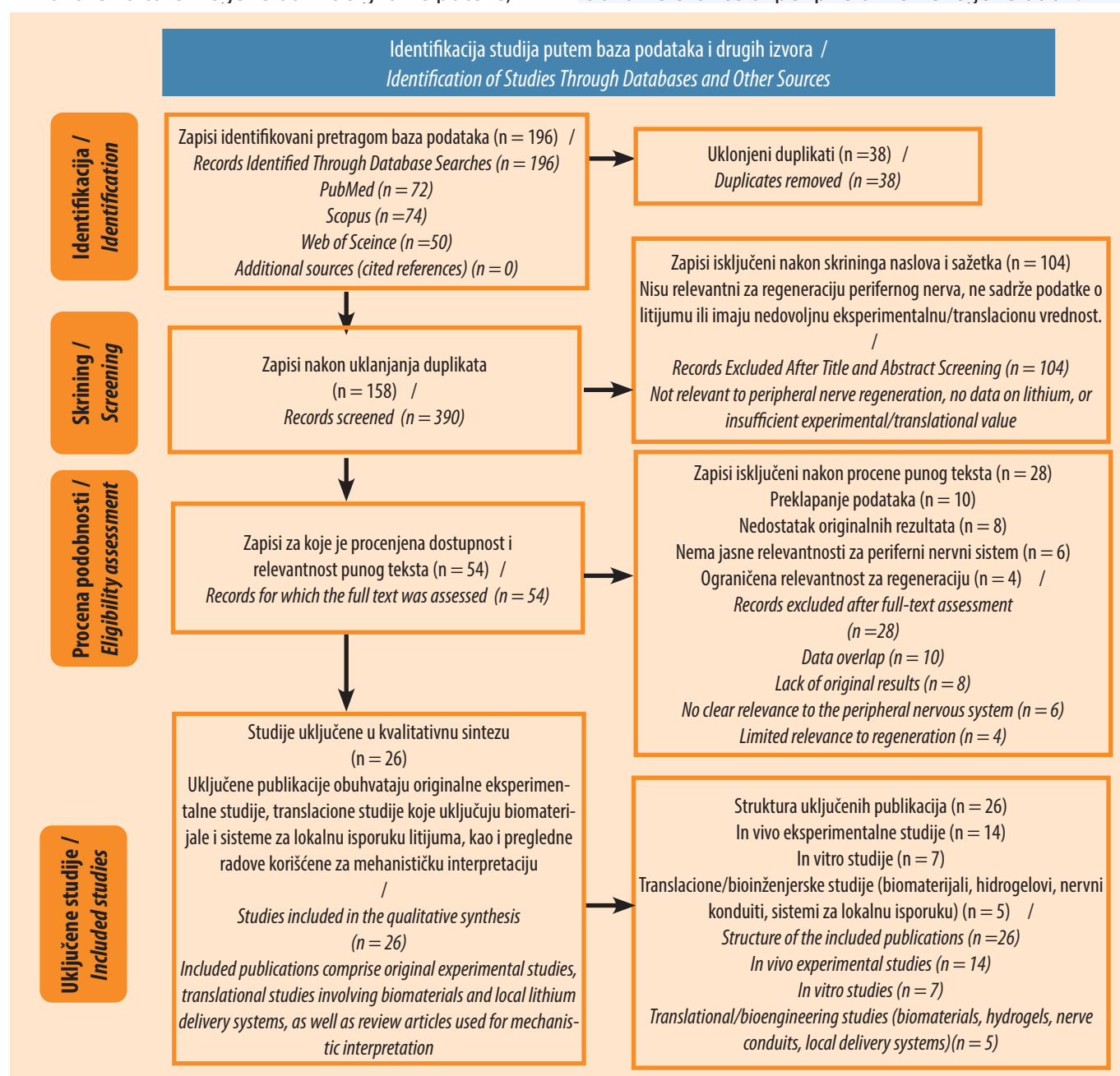
U konačnu kvalitativnu sintezu uključeno je 26 publikacija. Ovaj skup obuhvatao je originalne in vivo i in vitro eksperimentalne studije, translacione studije koje su analizirale biomaterijale i sisteme lokalne isporuke litijuma, kao i odabrane pregledne radove korišćene za interpretaciju mehanizama delovanja litijuma, biologije Švanovih ćelija i translacionog značaja regeneracije perifernih nerava.

Struktura uključenih publikacija obuhvatala je:

- 14 in vivo eksperimentalnih studija;
- 7 in vitro studija sa fokusom na Švanove ćelije, neuronske kulture i regenerativne signalne puteve;

Full-text analysis was conducted for 54 publications. During the eligibility assessment, an additional 28 papers were excluded due to overlapping data, lack of original findings, absence of a clear association with the peripheral nervous system, or limited relevance to regenerative processes following nerve injury.

Twenty-six publications were included in the final qualitative synthesis. The selected studies comprised original in vivo and in vitro experimental research, translational studies investigating biomaterials and localized lithium delivery systems, and selected review articles used to contextualize the mechanisms of action of lithium, Schwann cell biology, and the translational relevance of peripheral nerve regeneration.



Slika 1. PRISMA dijagram toka studija kroz faze identifikacije, selekcije i uključivanja. (PRISMA 2020 Flow Diagram).

Figure 1. PRISMA study flow diagram through the stages of identification, selection, and inclusion (PRISMA 2020 Flow Diagram).

- 5 translacionih i bioinženjerskih studija koje su analizirale biomaterijale, hidrogelove, nervne konduite i sisteme lokalne isporuke litijuma.

Proces identifikacije, selekcije, procene podobnosti i uključivanja studija prikazan je u PRISMA dijagramu (Slika 1).

REZULTATI

Neuroregenerativni i neuroprotektivni efekti litijuma u perifernom nervnom sistemu

Dostupna literatura ukazuje na to da litijum poseduje višestruke biološke efekte koji mogu biti relevantni za regeneraciju perifernih nerava, uključujući modulaciju neuronskog preživljavanja, aksonskog rasta i regenerativnog odgovora glijalnih ćelija [7,8]. Iako je prvobitno korišćen u psihijatriji, sve veći broj eksperimentalnih studija ukazuje na njegov širi neurobiološki potencijal, posebno u kontekstu regenerativne medicine [9].

U eksperimentalnim modelima povrede perifernih nerava, litijum je povezan sa poboljšanjem aksonske regeneracije i funkcionalnog oporavka, što je posebno istaknuto u studijama koje analiziraju njegov efekat na regeneraciju nakon traumatske lezije nerva [1]. Ovi efekti se povezuju sa njegovim delovanjem na intracelularne signalne puteve uključene u kontrolu neuronske plastičnosti i preživljavanja, pri čemu se posebno ističe inhibicija GSK-3 β i modulacija pro-survival signalizacije [10].

Pored direktnog uticaja na neurone, litijum ispoljava značajan efekat na glijalne ćelije, naročito Švanove ćelije, koje su ključne u procesu regeneracije perifernih nerava. In vitro studije pokazuju da litijum može stimulisati proliferaciju Švanovih ćelija uz istovremenu inhibiciju njihove migracije, što može doprineti stabilnijem regenerativnom mikrokruženju [11]. Ova promena ćelijskog ponašanja smatra se važnom za organizaciju regenerativnih puteva i podršku aksonskom rastu.

Dodatno, eksperimentalni podaci ukazuju na to da litijum utiče i na procese remijelinizacije, što je potvrđeno u modelima povrede nervnih korena, gde je uočeno poboljšanje funkcionalnog motornog oporavka nakon primene litijuma [3]. Ovi rezultati sugerišu da litijum ne deluje samo na fazu aksonskog rasta, već i na kasnije faze regeneracije, uključujući reorganizaciju mijelinske strukture. Značajan deo njegovog regenerativnog potencijala povezan je i sa indukcijom autofagije, koja je prepoznata kao važan mehanizam u održavanju ćelijske homeostaze i regenerativnog odgovora nakon nervne povrede. Studije ukazuju na to da aktivacija autofagije doprinosi neuroprotektivnim efektima litijuma i unapređuje funkcionalni oporavak nakon povrede nervnog sistema [12,13].

Iako većina dokaza potiče iz perifernih nervnih

The included publications comprised:

- 14 in vivo experimental studies;
- 7 in vitro studies focusing on Schwann cells, neuronal cultures, and regenerative signaling pathways;
- 5 translational and bioengineering studies investigating biomaterials, hydrogels, nerve conduits, and localized lithium delivery systems.

The process of study identification, selection, eligibility assessment, and inclusion is presented in the PRISMA flow diagram (Figure 1).

RESULTS

Neurodegenerative and neuroprotective effects of lithium in the peripheral nervous system

The available literature indicates that lithium exerts multiple biological effects that may be relevant to peripheral nerve regeneration, including the modulation of neuronal survival, axonal growth, and the regenerative responses of glial cells [7,8]. Although originally used in psychiatry, a growing body of experimental evidence suggests that it has broader neurobiological potential, particularly in the field of regenerative medicine [9].

In experimental models of peripheral nerve injury, lithium has been associated with enhanced axonal regeneration and improved functional recovery, with particularly notable effects reported in studies investigating its role following traumatic nerve injury [1]. These effects are associated with its influence on intracellular signaling pathways involved in the regulation of neuronal plasticity and survival, with inhibition of GSK-3 β and modulation of pro-survival signaling pathways being particularly prominent [10].

In addition to its direct effect on neurons, lithium exerts significant effects on glial cells, particularly Schwann cells, which play a central role in peripheral nerve regeneration. In vitro studies indicate that lithium can promote Schwann cell proliferation while simultaneously reducing their migratory activity, potentially contributing to the establishment of a more stable regenerative microenvironment [11]. This change in cellular behavior is thought to play an important role in the organization of regenerative pathways and the support of axonal growth.

Additionally, experimental evidence indicates that lithium may also influence remyelination processes, as demonstrated in nerve root injury models in which lithium administration was associated with improved functional motor recovery [3]. These findings suggest that lithium may influence not only axonal growth but also later stages of regeneration, including the reorganization of myelin structure. A substantial component of its regenerative potential may also be related

modela, deo mehanističkih uvida dolazi iz studija centralnog nervnog sistema, uključujući modele retinalne degeneracije i moždanog udara, gde je takođe zabeležen neuroprotektivni efekat litijuma [2,14]. Međutim, ovi rezultati se moraju tumačiti sa oprezom, s obzirom na fundamentalne razlike u regenerativnom kapacitetu centralnog i perifernog nervnog sistema.

Pored klasičnih farmakoloških oblika, novija istraživanja ukazuju i na potencijal savremenih formulacija litijuma, uključujući nano-strukturisane sisteme i biomaterijale, koji omogućavaju lokalizovano delovanje i produženo oslobađanje leka, čime se dodatno poboljšava njegov regenerativni efekat uz smanjenje sistemске izloženosti [15,16].

Uloga litijuma u funkciji Švanovih ćelija i procesu remijelinizacije

Švanove ćelije predstavljaju centralni celularni element regeneracije perifernog nervnog sistema, jer nakon povrede prolaze kroz proces fenotipske transformacije u tzv. stanje „popravke“ koje omogućava podršku aksonskom rastu, fagocitozu mijelinskih ostataka i formiranje regenerativnih puteva [4,5]. Ovaj adaptivni odgovor, iako visoko efikasan u ranoj fazi regeneracije, ostaje vremenski ograničen i podložan progresivnoj disfunkciji u uslovima produžene denervacije, što direktno kompromituje ishod nervne reparacije [6].

U ovom kontekstu, litijum se pojavljuje kao farmakološki modulatorski agens koji utiče na proliferativno i funkcionalno ponašanje Švanovih ćelija. In vitro studije pokazuju da litijum može značajno povećati proliferaciju Švanovih ćelija uz istovremenu supresiju njihove migracije, što se interpretira kao stabilizacija ćelijskog odgovora u regenerativnom mikrookruženju [11]. Ovakav efekat može doprineti efikasnijem usmeravanju regenerišućih aksona i očuvanju strukturalne organizacije regenerativnih traktova.

Pored uticaja na ćelijsku dinamiku, litijum ima značajnu ulogu u procesima remijelinizacije. U eksperimentalnom modelu povrede nervnih korena, primena litijuma je dovela do ubrzane remijelinizacije regenerišućih aksona, uz korelaciju sa poboljšanjem funkcionalnog motornog oporavka [3]. Ovi rezultati govore da litijum ne deluje isključivo na ranu fazu regeneracije, već i na kasniju fazu reorganizacije mijelinske ovojnice, što je ključno za obnovu brzine i efikasnosti nervne provodljivosti.

Dodatno, noviji podaci ukazuju na to da litijum može indirektno uticati na Švanove ćelije kroz modulaciju autofagije, čime se poboljšava njihova metabolička adaptacija i regenerativni kapacitet. Aktivacija autofagičnih puteva povezana je sa održavanjem ćelijske homeostaze i efikasnijim odgovorom na povredu, što dodatno doprinosi regeneraciji nervnog tkiva [12,13].

to the induction of autophagy, which is recognized as an important mechanism for maintaining cellular homeostasis and supporting the regenerative response following nerve injury. Studies suggest that autophagy activation contributes to the neuroprotective effects of lithium and may enhance functional recovery after nervous system injury [12,13].

Although most of the available evidence is derived from peripheral nerve models, some mechanistic insights come from studies of the central nervous system, including models of retinal degeneration and stroke, in which lithium has also demonstrated neuroprotective effects [2,14]. However, these findings should be interpreted with caution, given the fundamental differences in the regenerative capacity of the central and peripheral nervous systems.

In addition to conventional pharmacological formulations, recent research highlights the potential of advanced lithium delivery systems, including nano-structured formulations and biomaterials, which enable localized action and sustained drug release. These approaches may enhance the regenerative effects of lithium while minimizing systemic exposure [15,16].

The role of lithium in Schwann cell function and remyelination

Schwann cells are the central cellular mediators of peripheral nervous system regeneration. Following injury, they undergo phenotypic reprogramming into a so-called “repair” state that enables them to support axonal growth, facilitate the clearance of myelin debris through phagocytosis, and form regenerative pathways [4,5]. This adaptive response, although highly effective during the early stages of regeneration, is time-limited and progressively deteriorates with prolonged denervation, thereby compromising the overall outcome of nerve repair [6].

In this context, lithium appears to act as a pharmacological modulator of Schwann cell proliferation and function. In vitro studies indicate that lithium can significantly enhance Schwann cell proliferation while simultaneously suppressing their migratory activity, which may contribute to stabilization of the cellular response within the regenerative microenvironment [11]. This effect may contribute to more efficient guidance of regenerating axons and preservation of the structural organization of regenerative pathways.

In addition to modulating cellular dynamics, lithium appears to play a significant role in the remyelination process. In an experimental model of nerve root injury, lithium administration accelerated the remyelination of regenerating axons and was associated with improved functional motor recovery [3]. These findings indicate that lithium may influence not only the early

Savremeni pristupi takođe ukazuju na značaj kombinacije litijuma sa biomaterijalnim nosačima, pri čemu lokalna isporuka omogućava direktnu modulaciju Švanovih ćelija u zoni povrede. Biomaterijali kao što su hidrogelni sistemi i kompozitne strukture omogućavaju kontrolisano oslobađanje litijuma i stvaranje mikrookruženja pogodnog za Švanovu ćelijsku diferencijaciju i regeneraciju [15,16]. U takvim sistemima zabeležena je poboljšana interakcija između Švanovih ćelija i regenerišućih aksona, što dodatno podržava funkcionalni oporavak.

Sveukupno, dostupni podaci ukazuju na to da litijum deluje na više nivoa Švanove biologije, od proliferacije i fenotipske stabilizacije, preko regulacije autofagije, do podrške remijelinizaciji, čime se pozicionira kao potencijalni farmakološki modulatorski faktor u strategijama regeneracije perifernih nerava.

Eksperimentalni modeli i translacioni dokazi o efektima litijuma

Eksperimentalni dokazi o ulozi litijuma u regeneraciji nervnog sistema najvećim delom potiču iz in vivo modela povrede perifernih nerava, gde se procenjuju aksonski rast, remijelinizacija i funkcionalni oporavak nakon traume. U modelima avulzije i reimplantacije nervnih korenova, primena litijuma je bila povezana sa ubrzanjem funkcionalnog motornog oporavka, pri čemu se ovaj efekat dovodi u vezu sa poboljšanom remijelinizacijom regenerisanih aksona [3]. Ovi rezultati ukazuju na to da litijum može imati značajan uticaj ne samo na ranu fazu regeneracije, već i na kvalitet ponovnog uspostavljanja nervne provodljivosti.

U modelima povrede perifernog nerva kod glodara, dodatno je pokazano da kombinovana primena litijuma i neurotrofnih faktora, kao što je glijalni neurotrofni faktor (GDNF), može imati sinergistički efekat na regeneraciju nerva, što se ogleda u poboljšanoj reorganizaciji regenerativnih vlakana i funkcionalnom ishodu [17]. Ovi podaci sugerišu da se efekti litijuma mogu dodatno potencirati u kombinovanim terapijskim strategijama koje ciljaju više komponenti regenerativnog mikrookruženja.

Pored klasičnih modela perifernih nerava, deo eksperimentalnih dokaza potiče i iz studija na optičkom nervu i retinalnim ganglijskim ćelijama. U tim modelima litijum je bio povezan sa povećanim preživljavanjem ganglijskih ćelija i delimičnom stimulacijom aksonskog rasta nakon povrede optičkog nerva. Iako ovi nalazi potvrđuju neuroprotektivni potencijal litijuma, njihova direktna primena na periferne nerve mora se tumačiti sa oprezom zbog fundamentalnih razlika u regenerativnim sposobnostima centralnog i perifernog nervnog sistema [2,18].

phase of nerve regeneration but also the later stages of myelin sheath reorganization, which are crucial for restoring the speed and efficiency of nerve conduction.

Additionally, recent evidence suggests that lithium may indirectly influence Schwann cells by modulating autophagy, thereby enhancing their metabolic adaptation and regenerative capacity. Activation of autophagic pathways contributes to the maintenance of cellular homeostasis and promotes a more effective response to injury, further supporting peripheral nerve tissue regeneration [12,13].

Modern approaches also highlight the importance of combining lithium with biomaterial-based delivery systems, in which localized drug release enables direct modulation of Schwann cells at the site of injury. Biomaterials such as hydrogels and composite scaffolds can facilitate controlled lithium release while creating a regenerative microenvironment conducive to Schwann cell differentiation and peripheral nerve repair [15,16]. In such systems, enhanced interactions between Schwann cells and regenerating axons have been reported, further supporting functional recovery.

Overall, the available evidence indicates that lithium acts at multiple levels of Schwann cell biology, ranging from the regulation of proliferation and phenotypic stabilization to the modulation of autophagy and support of remyelination. These multifaceted effects position lithium as a potential pharmacological modulator in strategies aimed at promoting peripheral nerve regeneration.

Experimental models and translational evidence for the effects of lithium

Experimental evidence supporting a role for lithium in nervous system regeneration derives mostly from in vivo models of peripheral nerve injury, in which axonal growth, remyelination, and functional recovery after trauma are evaluated. In models of nerve root avulsion and reimplantation, lithium administration was associated with accelerated functional motor recovery, this effect being attributed to enhanced remyelination of regenerated axons [3]. These findings indicate that lithium may exert a significant influence not only during the early stages of regeneration but also on the quality of restored nerve conduction.

In rodent models of peripheral nerve injury, combined administration of lithium and neurotrophic factors, such as glial cell line-derived neurotrophic factor (GDNF), has further been shown to exert synergistic effects on nerve regeneration, as evidenced by enhanced reorganization of regenerating nerve fibers and improved functional outcomes [17]. These findings suggest that the effects of lithium may be further potentiated through

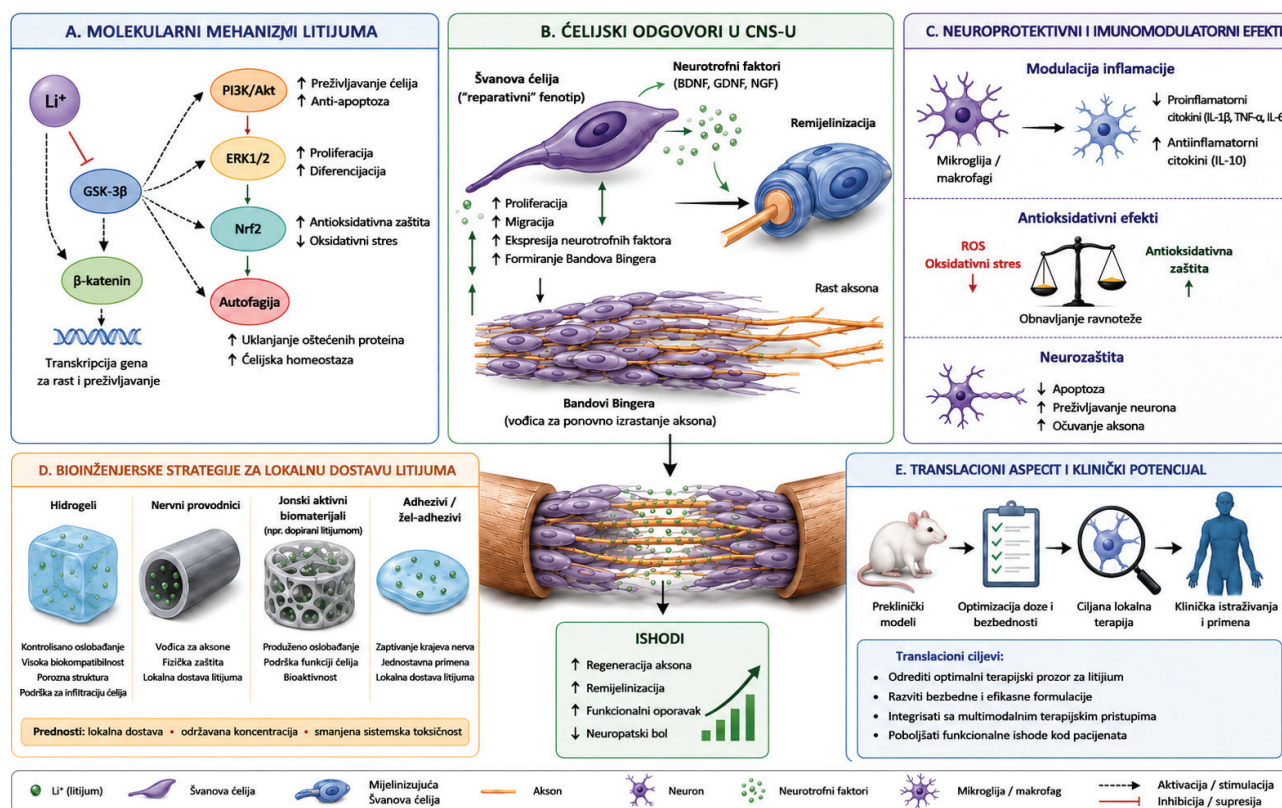
Dodatni translacioni uvidi potiču iz studija moždanog udara i spinalne povrede, gde je litijum pokazao sposobnost da modulira neuroinflamaciju i aktivira pro-survival signalne puteve, uključujući povećanje ekspresije miR-124 i inhibiciju GSK-3 β zavisnih i nezavisnih mehanizama. Iako ovi podaci nisu direktno vezani za periferne nerve, oni pružaju mehanističku osnovu za razumevanje šireg neuroprotektivnog delovanja litijuma [14].

U novijim istraživanjima naglasak se pomera ka bioinženjerskim strategijama koje omogućavaju lokalizovanu isporuku litijuma u zoni povrede. Upotreba adhezivnih sistema i biomaterijala sa inkorporiranim litijumom pokazala je poboljšanje regeneracije aksona i ponovnog uspostavljanja nervnog kontinuiteta u eksperimentalnim modelima transekcije nerva. Slično tome, primena hidrogelnih i kompozitnih sistema omogućava stvaranje stabilnog mikrookruženja koje podržava regeneraciju i funkciju ćelija uključenih u proces oporavka [15,16].

combination therapeutic strategies targeting multiple components of the regenerative microenvironment.

In addition to classical models of peripheral nerve injury, experimental evidence has also been derived from studies of the optic nerve and retinal ganglion cells. In these models, lithium administration was associated with increased ganglion cell survival and partial stimulation of axonal growth following optic nerve injury. Although these findings further support the neuroprotective potential of lithium, their direct extrapolation to peripheral nerve regeneration should be interpreted with caution, given the fundamental differences in the regenerative capacities of the central and peripheral nervous systems [2,18].

Additional translational insights come from studies of stroke and spinal cord injury, in which lithium has been shown to modulate neuroinflammatory responses and activate pro-survival signaling pathways, including the upregulation of miR-124 expression and the inhibition of both GSK-3 β -dependent and GSK-3 β -in-



Slika 2. Mehanički pregled uloge litijuma u regeneraciji perifernih nerava.

Prikazani su ključni molekularni, ćelijski i translacioni mehanizmi delovanja litijuma u regeneraciji perifernog nervnog sistema. Litijum inhibicijom GSK-3 β i modulacijom signalnih puteva PI3K/Akt, ERK1/2 i β -katenina podstiče ćelijsko preživljavanje, neuroplastičnost, proliferaciju Švanovih ćelija i aksonalni rast. Pored toga, aktivacijom autofagije, smanjenjem oksidativnog stresa i regulacijom neuroinflamacije stvara povoljno mikrookruženje za regeneraciju nervnog tkiva. Savremene bioinženjerske strategije, uključujući hidrogelove, nervne konduite, jonski aktivne biomaterijale i bioadhezive sa litijumom, omogućavaju lokalnu i kontrolisanu isporuku litijuma na mestu povrede, što može doprineti efikasnijoj remijelinizaciji, funkcionalnom oporavku i smanjenju sistemske toksičnosti.

Napomena: Slika je generisana korišćenjem alata zasnovanih na veštačkoj inteligenciji za potrebe vizuelne sinteze dostupnih naučnih podataka i naknadno pregledana i prilagođena od strane autora u skladu sa literaturom analiziranom u ovom radu. Prikaz služi isključivo kao konceptualna ilustracija i ne predstavlja originalne eksperimentalne rezultate.

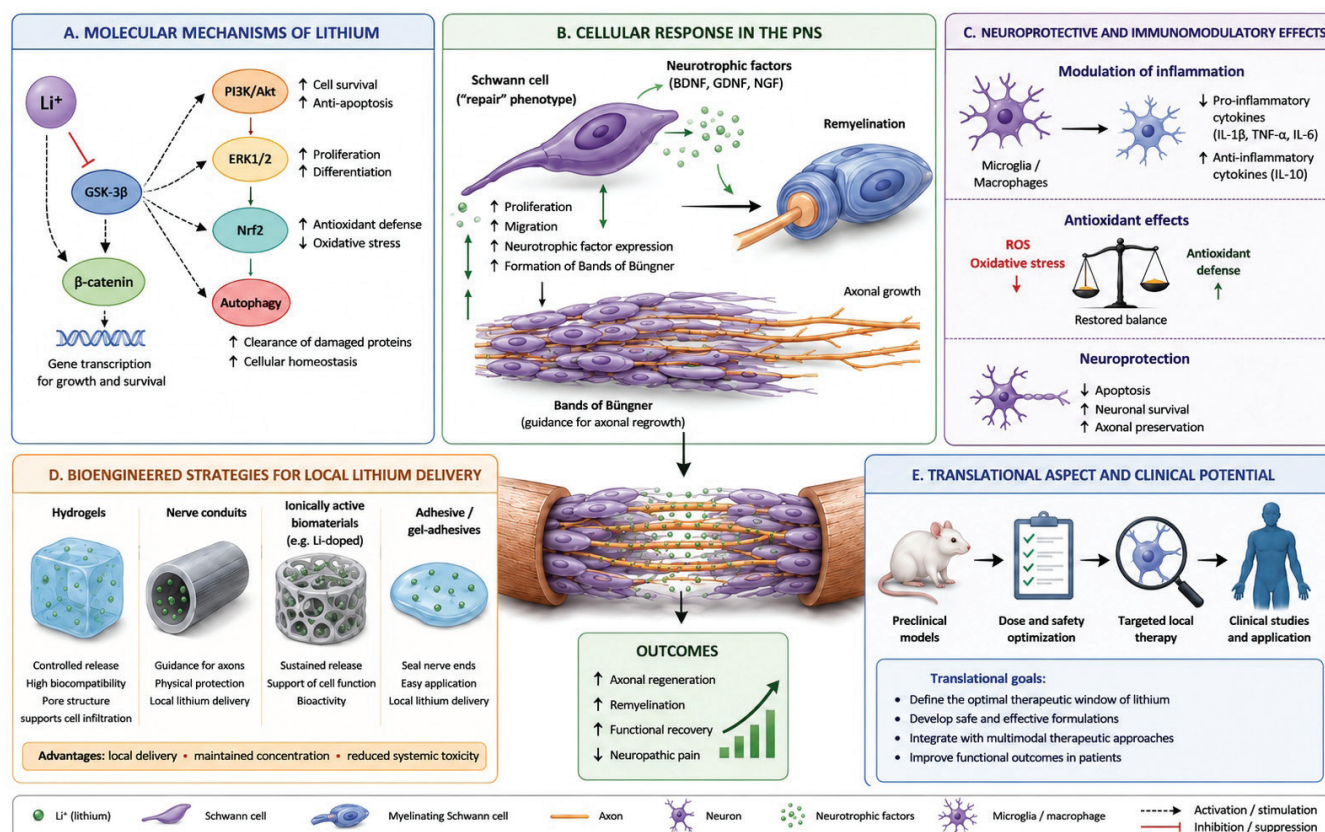


Figure 2. A mechanistic overview of the role of lithium in peripheral nerve regeneration.

The key molecular, cellular, and translational mechanisms of lithium action in peripheral nervous system regeneration are presented. By inhibiting GSK-3 β and modulating the PI3K/Akt, ERK1/2, and β -catenin signaling pathways, lithium promotes cell survival, neuroplasticity, Schwann cell proliferation, and axonal growth. In addition, by activating autophagy, reducing oxidative stress, and regulating neuroinflammation, it creates a favorable microenvironment for nerve tissue regeneration. Modern bioengineering strategies, including hydrogels, nerve conduits, ionically active biomaterials, and lithium-containing bioadhesives, enable the local and controlled delivery of lithium at the site of injury, which may contribute to more efficient remyelination, functional recovery, and reduced systemic toxicity.

Note: The image was generated using artificial intelligence-based tools for the visual synthesis of available scientific data and was subsequently reviewed and adjusted by the authors in accordance with the literature analyzed in this paper. The image is intended solely as a conceptual illustration and does not represent original experimental results.

U širem kontekstu, savremeni biomaterijali kao što su hidrogelovi i konduiti sa jonskom provodljivošću dodatno doprinose optimizaciji lokalne isporuke i biološke kompatibilnosti regenerativnih sistema, čime se otvara mogućnost precizne kontrole mikrookruženja nervne regeneracije [19].

Sveukupno posmatrano, eksperimentalni podaci ukazuju na to da litijum pokazuje konzistentne neuroregenerativne i neuroprotektivne efekte u različitim modelima, pri čemu su najizraženiji rezultati uočeni u perifernim nervnim modelima i u kombinaciji sa bioinženjerskim strategijama lokalne isporuke. Sažeti prikaz najvažnijih molekularnih, ćelijskih i tkivnih mehanizama putem kojih litijum doprinosi regeneraciji perifernih nerava prikazan je na Slici 2.

Molekularni mehanizmi delovanja litijuma u regeneraciji perifernih nerava

Molekularni efekti litijuma predstavljaju osnovu njegovog neuroprotektivnog i neuroregenerativnog poten-

dependent mechanisms. Although these findings are not directly related to peripheral nerve regeneration, they provide a mechanistic basis for understanding the broader neuroprotective effects of lithium [14].

Recent research has increasingly focused on bioengineering strategies that enable the localized delivery of lithium to the site of nerve injury. The use of lithium-incorporated adhesive systems and biomaterials has been shown to enhance axonal regeneration and facilitate the restoration of nerve continuity in experimental models of nerve transection. Similarly, hydrogel-based and composite systems can establish a stable microenvironment that supports the regeneration and functional activity of cells involved in the recovery process [15,16].

In a broader context, advanced biomaterials, including hydrogels and ionically conductive nerve conduits, may further optimize the localized delivery and biocompatibility of regenerative systems, thereby offering the potential for precise modulation of the microenvironment during nerve regeneration [19].

cijala. Iako je litijum decenijama korišćen kao stabilizator raspoloženja u psihijatriji, savremena istraživanja pokazala su da njegovo delovanje obuhvata veliki broj intracelularnih signalnih puteva uključenih u preživljavanje neurona, aksonski rast, plastičnost nervnog sistema i odgovor glijalnih ćelija na povredu [7,8].

Najistraženiji mehanizam delovanja litijuma jeste inhibicija glikogen sintaza kinaze-3 β (GSK-3 β), enzima koji ima centralnu ulogu u regulaciji ćelijskog rasta, diferencijacije i apoptotskih procesa. Inhibicijom GSK-3 β dolazi do aktivacije Wnt/ β -katenin signalnog puta, što rezultuje povećanom ekspresijom gena odgovornih za ćelijsko preživljavanje, proliferaciju i regeneraciju nervnog tkiva [9,10]. Aktivacija ovog signalnog sistema posebno je značajna nakon povrede nerva, kada je neophodno obezbediti održavanje regenerativnog fenotipa Švanovih ćelija i stimulisati produžavanje aksona.

Pored GSK-3 β signalizacije, litijum utiče i na PI3K/Akt i ERK1/2 puteve, koji predstavljaju ključne regulatorne sisteme ćelijskog preživljavanja. Aktivacijom ovih signalnih kaskada povećava se otpornost neurona na oksidativni stres i smanjuje aktivacija proapoptotskih mehanizama, čime se stvara povoljnije mikrookruženje za regeneraciju [7,10]. Ovakvi efekti imaju poseban značaj u ranim fazama nakon povrede kada sekundarna degeneracija može značajno ograničiti regenerativni potencijal nerva.

Jedan od najznačajnijih molekularnih efekata litijuma odnosi se na regulaciju ekspresije antiapoptotskog proteina Bcl-2. Sprovedena studija pokazala je da litijum povećava ekspresiju Bcl-2, što rezultuje povećanim preživljavanjem neurona i stimulacijom aksonske regeneracije nakon povrede optičkog nerva [2]. Ovi rezultati kasnije su potvrđeni i u drugim modelima nervnog oštećenja, sugerišući da Bcl-2 predstavlja jednu od ključnih molekularnih karika preko kojih litijum ostvaruje svoje neuroprotektivne efekte.

Poslednjih godina posebna pažnja usmerena je na ulogu autofagije u regeneraciji nervnog sistema. Autofagija omogućava uklanjanje oštećenih organela i proteinskih agregata, čime doprinosi održavanju ćelijske homeostaze i metaboličke stabilnosti. Litijum aktivira autofagične procese putem mehanizama koji delimično zavise od inhibicije inozitol-monofosfataze i modulacije mTOR signalizacije [13]. Eksperimentalne studije pokazale su da ovakva aktivacija autofagije doprinosi očuvanju funkcije Švanovih ćelija, povećava otpornost neurona na stres i poboljšava funkcionalni oporavak nakon povrede nervnog sistema [12,16].

Dodatno, litijum pokazuje sposobnost regulacije neuroinflamatornih procesa. Nakon povrede perifernog nerva aktiviraju se brojni inflamatorni medijatori koji mogu imati i protektivne i štetne efekte. Litijum

Taken together, the experimental evidence indicates that lithium exerts consistent neuroregenerative and neuroprotective effects across a range of experimental models, with the most pronounced effects observed in peripheral nerve injury models and in combination with bioengineered strategies for localized delivery. A summary of the principal molecular, cellular, and tissue-level mechanisms through which lithium contributes to peripheral nerve regeneration is presented in Figure 2.

Molecular mechanisms underlying the effects of lithium on peripheral nerve regeneration

The molecular effects of lithium are the basis of its neuroprotective and neuroregenerative potential. Although lithium has been used as a mood stabilizer in psychiatry for decades, contemporary research has demonstrated that its effects involve multiple intracellular signaling pathways that regulate neuronal survival, axonal growth, nervous system plasticity, and glial responses to injury [7,8].

The most extensively investigated mechanism of lithium action is the inhibition of glycogen synthase kinase-3 β (GSK-3 β), an enzyme that plays a central role in regulating cellular growth, differentiation, and apoptotic processes. Inhibition of GSK-3 β activates the Wnt/ β -katenin signaling pathway, thereby promoting the expression of genes involved in cell survival, proliferation, and neural tissue regeneration [9,10]. Activation of this signaling pathway is particularly important following nerve injury, when the maintenance of the regenerative phenotype of Schwann cells and the stimulation of axonal elongation are essential for effective nerve regeneration.

In addition to GSK-3 β signaling, lithium also modulates the PI3K/Akt and ERK1/2 pathways, which constitute key regulatory systems governing cellular survival. Activation of these signaling cascades enhances neuronal resistance to oxidative stress and attenuates pro-apoptotic mechanisms, thereby creating a more favorable microenvironment for nerve regeneration [7,10]. These effects are particularly important during the early stages following nerve injury, when secondary degeneration can substantially compromise the regenerative capacity of the nerve.

One of the most significant molecular effects of lithium involves the regulation of the anti-apoptotic protein Bcl-2. Studies have demonstrated that lithium increases Bcl-2 expression, thereby promoting neuronal survival and stimulating axonal regeneration following optic nerve injury [2]. These findings were subsequently corroborated in other models of nerve injury, suggesting that Bcl-2 represents a key molecular mediator through which lithium exerts its neuroprotective effects.

utiče na ekspresiju mikroRNK, posebno miR-124, koja učestvuje u kontroli neuroinflamatornog odgovora i smanjenju ekspresije proinflamatornih transkripcijskih faktora [14]. Time se omogućava uspostavljanje povoljnijeg regenerativnog mikrokruženja koje podržava aksonski rast i remijelinizaciju.

Posmatrano u celini, litijum deluje kao višeciljni molekularni regulator koji istovremeno moduliše procese ćelijskog preživljavanja, plastičnosti, autofagije, neuroinflamacije i regeneracije. Upravo ova sposobnost integracije različitih bioloških puteva razlikuje litijum od većine konvencionalnih neuroprotektivnih agenasa i predstavlja osnovu njegovog potencijala u regenerativnoj medicini perifernog nervnog sistema.

Biomaterijali i sistemi lokalne isporuke litijuma

Jedan od glavnih izazova u translaciji litijuma iz eksperimentalnih modela u kliničku praksu jeste postizanje dovoljne koncentracije u zoni povrede uz istovremeno minimiziranje sistemske izloženosti i mogućih neželjenih efekata. Zbog toga se poslednjih godina intenzivno razvijaju bioinženjerski sistemi za lokalnu i kontrolisanu isporuku litijuma, koji omogućavaju produženo oslobađanje leka direktno u regenerativnom mikrokruženju [15,20].

Među najperspektivnijim pristupima izdvajaju se hidrogelni sistemi. Hidrogelovi predstavljaju trodimenzionalne biomaterijalne mreže sposobne da apsorbuju velike količine vode i istovremeno obezbede fizičku podršku ćelijama uključenim u regeneraciju. Babaei i saradnici pokazali su da kompozitni hidrogelovi sa inkorporiranim litijum-hloridom mogu stimulisati proliferaciju neuralnih matičnih ćelija, njihovu diferencijaciju i rast neurita, stvarajući mikrokruženje pogodno za regeneraciju nervnog tkiva [20]. Kontrolisano oslobađanje litijuma iz hidrogelova omogućava dugotrajan biološki efekat bez potrebe za visokim sistemskim dozama.

Pored hidrogelova, značajan napredak ostvaren je u razvoju adhezivnih biomaterijala. Bu i saradnici razvili su bioadhezivnu platformu zasnovanu na poli(e-tilen-glikolu) sa inkorporiranim litijumom, koja omogućava povezivanje presečenih nervnih segmenata uz istovremeno lokalno oslobađanje jona litijuma [15]. U eksperimentalnim modelima ovaj sistem doveo je do značajnog poboljšanja aksonske regeneracije i funkcionalnog oporavka. Savremeni trendovi uključuju i upotrebu nanomaterijala kao nosača litijuma. Primer su upravo karbonizovane polimerne nanočestice dopirane litijumom koje aktiviraju autofagiju Švanovih ćelija i pospešuju regeneraciju perifernih nerava [16]. Ovakvi sistemi omogućavaju precizniju kontrolu kinetike oslobađanja litijuma i potencijalno smanjenje sistemske toksičnosti.

In recent years, increasing attention has been directed toward the role of autophagy in nervous system regeneration. Autophagy facilitates the removal of damaged organelles and protein aggregates, thereby contributing to the maintenance of cellular homeostasis and metabolic stability. Lithium promotes autophagic activity through mechanisms that are partially dependent on the inhibition of inositol monophosphatase and modulation of mTOR signaling [13]. Experimental studies have demonstrated that activation of autophagy contributes to the preservation of Schwann cell function, enhances neuronal resistance to cellular stress, and promotes functional recovery following nervous system injury [12,16].

Additionally, lithium has been shown to modulate neuroinflammatory processes. Following peripheral nerve injury, numerous inflammatory mediators are activated, exerting both protective and detrimental effects. Lithium influences the expression of microRNAs, particularly miR-124, which plays a role in regulating the neuroinflammatory response and suppressing the expression of pro-inflammatory transcription factors [14]. This contributes to the establishment of a more favorable regenerative microenvironment that supports axonal growth and remyelination.

Taken together, the available evidence indicates that lithium functions as a multi-target molecular regulator, simultaneously modulating cellular survival, plasticity, autophagy, neuroinflammation, and regenerative processes. This capacity to influence multiple interconnected biological pathways distinguishes lithium from many conventional neuroprotective agents and underpins its potential application in the regenerative medicine of the peripheral nervous system.

Biomaterials and localized lithium delivery systems

One of the main challenges in translating lithium from experimental models to clinical practice lies in achieving adequate lithium concentrations at the site of injury while minimizing systemic exposure and the associated risk of adverse effects. Consequently, recent years have witnessed intensive development of bioengineering-based systems for the localized and controlled delivery of lithium, designed to facilitate its sustained release directly within the regenerative microenvironment [15,20].

Hydrogel-based systems represent one of the most promising approaches in this field. Hydrogels are three-dimensional biomaterial networks capable of absorbing substantial amounts of water while simultaneously providing structural support for cells involved in tissue regeneration. Babaei et al. demonstrated that composite hydrogels incorporating lithium chloride can

Posebnu pažnju privukli su grafenski biomaterijali zbog svojih mehaničkih, električnih i bioloških karakteristika. Grafenski kompoziti mogu služiti kao provodljive platforme koje istovremeno podržavaju rast neurita i omogućavaju inkorporaciju bioaktivnih molekula, uključujući litijum [19,21]. Slično tome, savremena istraživanja nanomaterijala ukazuju na to da kombinacija litijuma sa nano-strukturisanim biomaterijalima može dodatno stimulirati neuritogenezu i ćelijsku diferencijaciju [20,22].

Novi razvojni pravac predstavljaju jonski provodljivi nervni konduiti. Huang i saradnici pokazali su da hidrogelom ispunjeni konduiti sa sposobnošću jonske provodljivosti stvaraju mikrokruženje koje oponaša fiziološke karakteristike nervnog tkiva i značajno poboljšavaju regeneraciju perifernih nerava [19]. Integracija litijuma u ovakve sisteme mogla bi predstavljati sledeći korak u razvoju inteligentnih biomaterijala za regenerativnu medicinu.

Sveukupno, biomaterijali omogućavaju prelazak sa sistemske primene litijuma ka preciznoj lokalnoj terapiji. Kombinacija kontrolisanog oslobađanja, biokompatibilnosti i sposobnosti modulacije ćelijskog mikrokruženja čini ove sisteme jednim od najvažnijih translacionih pravaca budućeg razvoja regenerativnih terapija perifernih nerava.

Kombinovane i sinergističke regenerativne strategije: litijum kao centralni neuromodulator

Savremeni koncept regenerativne medicine sve više napušta pristup zasnovan na pojedinačnim terapijskim agensima i usmerava se ka kombinovanim strategijama koje simultano deluju na više bioloških mehanizama uključenih u regeneraciju nervnog tkiva. U tom kontekstu litijum se izdvaja kao posebno zanimljiv kandidat zbog svoje sposobnosti da istovremeno moduliše neuronsko preživljavanje, Švanovu ćelijsku plastičnost, neuroinflamaciju, autofagiju i remijelinizaciju [1,10,13].

Jedan od prvih dokaza o potencijalnoj sinergiji litijuma sa drugim regenerativnim pristupima prikazan je u studiji Lin i saradnika, gde je kombinacija litijum-hlorida i GDNF-a dovela do izraženijeg aksonskog rasta i funkcionalnog oporavka u odnosu na pojedinačne terapije. Ovi rezultati ukazuju na to da litijum može pojačavati efekte neurotrofičnih faktora i time doprineti stvaranju efikasnijeg regenerativnog mikrokruženja [17].

Posebno značajan doprinos ovom konceptu predstavlja hipoteza trojne neuromodulatorne ose. U ovom modelu litijum se posmatra kao centralni regulator koji deluje sinergistički sa ekstraktima gljive *Hericium erinaceus* i vitaminom B12. Prema ovoj hipotezi, svaka od tri komponente cilja različite, ali međusobno povezane biološke procese. Litijum dominantno moduliše intra-

stimulate the proliferation and differentiation of neural stem cells, as well as neurite outgrowth, thereby establishing a microenvironment suitable for nerve tissue regeneration [20]. Controlled lithium release from hydrogel-based systems enables long-lasting biological effect while minimizing the need for high systemic doses.

In addition to hydrogels, considerable progress has been made in the development of adhesive biomaterials. Bu et al. developed a bioadhesive platform based on lithium-incorporated poly(ethylene glycol), which enables the approximation and connection of severed nerve segments while simultaneously providing localized release of lithium ions [15]. In experimental models, this system led to significant improvements in axonal regeneration and functional recovery. Contemporary approaches also include the use of nanomaterials as lithium carriers. One such example is represented by carbonized polymer nanoparticles doped with lithium, which activate autophagy in Schwann cells and promote peripheral nerve regeneration [16]. These systems offer more precise control over lithium release kinetics and may thereby contribute to reducing systemic toxicity.

Graphene-based biomaterials have attracted particular attention owing to their mechanical, electrical, and biological properties. Graphene composites can function as conductive platforms that support neurite outgrowth while also enabling the incorporation of bioactive molecules, including lithium [19,21]. Similarly, current research on nanomaterials indicates that combining lithium with nanostructured biomaterials can further enhance neuritogenesis and cellular differentiation [20,22].

A further emerging direction involves the development of ion-conducting nerve conduits. Huang et al. demonstrated that hydrogel-filled conduits with ionic conductivity create a microenvironment that mimics the physiological characteristics of nerve tissue and significantly enhances peripheral nerve regeneration [19]. The integration of lithium into such systems could represent a further step in the development of intelligent biomaterials for regenerative medicine.

Overall, biomaterials facilitate the transition from systemic lithium administration to precise local therapy. The combination of controlled release, biocompatibility, and the capacity to modulate the cellular microenvironment makes these systems one of the most important translational directions for the future development of peripheral nerve regenerative therapies.

Combined and Synergistic Regenerative Strategies: Lithium as a Central Neuromodulator

The contemporary concept of regenerative medicine is increasingly moving beyond the use of individual therapeutic agents toward combined strategies that

celularnu signalizaciju, autofagiju i ćelijsko preživljavanje; *Hericium erinaceus* stimuliše sintezu neurotrofičnih faktora i neuritogenezu; vitamin B12 podržava remijelinizaciju, metabolički integritet neurona i regeneraciju nervnog vlakna [23].

Koncept trojne neuromodulatorne ose posebno je značajan jer prevazilazi tradicionalni redukcionistički pristup regeneraciji perifernih nerava. Umesto fokusiranja na jedan signalni put ili jednu ćelijsku populaciju, predloženi model integriše više nivoa biološke organizacije, od molekularnih signalnih mreža do funkcionalnog oporavka nerva. Takav pristup je u skladu sa savremenim shvatanjem da uspešna regeneracija zahteva koordinisanu interakciju neurona, Švanovih ćelija, imunoloških ćelija i ekstracelularnog matriksa [4,6].

Dodatni potencijal ovakvih kombinovanih strategija proizlazi iz mogućnosti njihove integracije sa savremenim biomaterijalima. Litijum, neurotrofični faktori i metabolički modulatori mogu se inkorporirati u hidrogelove, nervne konduite ili nano-strukturisane sisteme za lokalnu isporuku, čime se postiže prostorno i vremenski kontrolisana terapijska aktivnost. Na taj način moguće je objediniti farmakološku modulaciju i bioinženjersku podršku regenerativnom procesu [15,19,20].

Posmatrano iz translacione perspektive, litijum se sve više pozicionira ne samo kao samostalni neuroregenerativni agens, već kao centralna komponenta multimodalnih terapijskih strategija. Njegova sposobnost da poveže neurotrofične, metaboličke, glijalne i imunološke mehanizme čini ga pogodnim kandidatom za razvoj sledeće generacije personalizovanih regenerativnih terapija. U tom smislu, hipoteza trojne neuromodulatorne ose predstavlja važan teorijski okvir za buduća eksperimentalna i klinička istraživanja usmerena ka optimizaciji oporavka nakon povreda perifernih nerava.

DISKUSIJA

Rezultati ovog sistematskog pregleda ukazuju na to da litijum predstavlja jedan od najperspektivnijih farmakoloških modulatora regeneracije perifernih nerava među trenutno dostupnim eksperimentalnim terapijama. Za razliku od pristupa koji ciljaju pojedinačne komponente regenerativnog odgovora, litijum deluje na više međusobno povezanih bioloških nivoa, uključujući preživljavanje neurona, plastičnost Švanovih ćelija, remijelinizaciju, aksonalni rast, autofagiju i regulaciju inflamatornog odgovora [1,7–10,13].

Ovakva multimodalnost može predstavljati značajnu prednost u poređenju sa strategijama koje se oslanjaju isključivo na neurotrofne faktore ili biomaterijalne platforme. Jedan od najkonzistentnijih rezultata analiziranih studija odnosi se na uticaj litijuma na Švanove ćelije, koje predstavljaju centralne efektorske

simultaneously target multiple biological mechanisms involved in nerve tissue regeneration. In this context, lithium represents a particularly promising candidate owing to its ability to simultaneously modulate neuronal survival, Schwann cell plasticity, neuroinflammation, autophagy, and remyelination [1,10,13].

One of the earliest indications of the potential synergy between lithium and other regenerative approaches was provided by a study by Lin et al., in which the combination of lithium chloride and GDNF resulted in more pronounced axonal growth and functional recovery compared with either treatment alone. These findings indicate that lithium may enhance the effects of neurotrophic factors and thereby contribute to the development of a more effective regenerative microenvironment [17].

A particularly significant contribution to this concept is the hypothesis of a triple neuromodulatory axis. Within this model, lithium is regarded as a central regulator that acts synergistically with extracts of the mushroom *Hericium erinaceus* and vitamin B12. According to this hypothesis, each of the three components targets distinct but interrelated biological processes. Lithium predominantly modulates intracellular signaling, autophagy, and cell survival; *Hericium erinaceus* stimulates the synthesis of neurotrophic factors and neuritogenesis; and vitamin B12 supports remyelination, neuronal metabolic integrity, and nerve fiber regeneration [23].

The concept of the triple neuromodulatory axis is particularly significant because it extends beyond the traditional reductionist approach to peripheral nerve regeneration. Rather than focusing on a single signaling pathway or cell population, the proposed model integrates multiple levels of biological organization, ranging from molecular signaling networks to functional nerve recovery. This approach is consistent with the contemporary understanding that successful regeneration requires coordinated interactions among neurons, Schwann cells, immune cells, and the extracellular matrix [4,6].

The further potential of such combined strategies lies in their integration with modern biomaterials. Lithium, neurotrophic factors, and metabolic modulators can be incorporated into hydrogels, nerve conduits, or nanostructured systems for local delivery, thereby enabling spatially and temporally controlled therapeutic activity. In this way, pharmacological modulation can be combined with bioengineering support for the regenerative process [15,19,20].

From a translational perspective, lithium is increasingly regarded not only as a stand-alone neuroregenerative agent but also as a central component of multimodal therapeutic strategies. Its ability to influence neurotrophic, metabolic, glial, and immune mechanisms

ćelije regeneracije perifernih nerava. Nakon povrede nerva, Švanove ćelije prolaze kroz proces dediferencijacije i prelaska u reparativni fenotip koji omogućava uklanjanje ostataka mijelina, lučenje neurotrofnih faktora i usmeravanje regenerišućih aksona [4–6].

Jedna studiji je pokazala da litijum povećava proliferaciju Švanovih ćelija i istovremeno reguliše njihovu migraciju, čime doprinosi formiranju organizovanog regenerativnog mikrokruženja [11]. Ovi rezultati su dodatno potvrđeni studijama koje ukazuju na to da litijum aktivira autofagiju u Švanovim ćelijama i na taj način održava njihovu funkcionalnu stabilnost tokom procesa reparacije [16]. Posmatrano zajedno, dostupni dokazi ukazuju na to da Švanove ćelije predstavljaju jednu od glavnih ćelijskih meta regenerativnog delovanja litijuma.

Pored efekata na glijalne ćelije, litijum direktno utiče i na neurone i regeneraciju aksona. Ključni molekularni mehanizam povezan je sa inhibicijom glikogen-sintaza-kinaze-3 β (GSK-3 β), što dovodi do aktivacije Wnt/ β -catenin signalizacije, povećane ekspresije Bcl-2 proteina i stimulacije puteva odgovornih za ćelijsko preživljavanje i rast aksona [2,9,10]. Pojedine studije su pokazale da litijum ubrzava funkcionalni oporavak nakon avulzije ventralnog korena kroz unapređenje remijelinizacije i regeneracije aksona [3], dok je Kuffler istakao da litijum deluje istovremeno na neurone i ćelije mikrokruženja, čime povećava verovatnoću uspostavljanja funkcionalnih nervnih veza nakon povrede [1]. Iako deo ovih mehanističkih saznanja potiče iz modela centralnog nervnog sistema, uključujući retinu i optički nerv [2,18], osnovni signalni putevi uključeni u neuroprotekciju i aksonalni rast pokazuju visok stepen konzerviranosti i verovatno imaju značaj i u perifernom nervnom sistemu.

Savremena istraživanja dodatno ukazuju na to da regenerativni efekti litijuma ne zavise samo od direktne stimulacije ćelijskog rasta, već i od njegove sposobnosti da reguliše ćelijsku homeostazu i energetske metabolizam. Litijum aktivira autofagiju i pospešuje uklanjanje oštećenih organela, čime poboljšava otpornost neurona i Švanovih ćelija tokom perioda intenzivne regeneracije [12,13]. Istovremeno, modulacijom PI3K/Akt, ERK1/2 i CREB/BDNF puteva doprinosi održavanju neurotrofne signalizacije i metaboličke stabilnosti [10,14]. Ovakav integrativni efekat može objasniti zbog čega litijum pokazuje regenerativni potencijal u različitim modelima neurološkog oštećenja.

Poseban značaj analiziranih studija ogleda se u činjenici da se poslednjih godina fokus istraživanja pomera sa sistemske primene litijuma ka lokalnim bioinženjerskim sistemima isporuke. Ovakav pristup predstavlja direktan odgovor na jedno od najvećih

makes it a suitable candidate for the development of next-generation personalized regenerative therapies. In this context, the triple neuromodulatory axis hypothesis represents an important theoretical framework for future experimental and clinical research aimed at optimizing recovery following peripheral nerve injuries.

DISCUSSION

The findings of this systematic review indicate that lithium represents one of the most promising pharmacological modulators of peripheral nerve regeneration among currently available experimental therapies. Unlike approaches that target individual components of the regenerative response, lithium acts across multiple interrelated biological processes, including neuronal survival, Schwann cell plasticity, remyelination, axonal growth, autophagy, and regulation of the inflammatory response [1,7–10,13].

Such multimodal activity may represent a significant advantage over strategies that rely solely on neurotrophic factors or biomaterial platforms. One of the most consistent findings across the analyzed studies concerns the effect of lithium on Schwann cells, which represent key effector cells in peripheral nerve regeneration. Following nerve injury, Schwann cells undergo dedifferentiation and transition to a reparative phenotype that facilitates the removal of myelin remnants, the secretion of neurotrophic factors, and the guidance of regenerating axons [4–6].

One study demonstrated that lithium increases Schwann cell proliferation while simultaneously regulating their migration, thereby contributing to the formation of an organized regenerative microenvironment [11]. These findings were further supported by studies indicating that lithium activates autophagy in Schwann cells, thereby maintaining their functional stability during the repair process [16]. Taken together, the available evidence indicates that Schwann cells represent one of the principal cellular targets of lithium's regenerative effects.

In addition to its effects on glial cells, lithium directly influences neurons and axonal regeneration. A key molecular mechanism involves the inhibition of glycogen synthase kinase-3 β (GSK-3 β), resulting in activation of Wnt/ β -catenin signaling, increased expression of Bcl-2 proteins, and stimulation of pathways involved in cell survival and axonal growth [2,9,10]. Several studies have shown that lithium accelerates functional recovery following ventral root avulsion by promoting remyelination and axonal regeneration [3], while Kuffler reported that lithium acts simultaneously on neurons and cells within the microenvironment, thereby by increasing the likelihood of establishing functional

ograničenja kliničke primene litijuma – njegov uski terapijski prozor i mogućnost razvoja renalne, endokrine i neurološke toksičnosti pri dugotrajnoj sistemskej ekspoziciji [2,16,17]. Litijum-ugrađeni bioadhezivi, hidrogelovi, nanočestice i nervni konduiti omogućavaju postizanje visokih lokalnih koncentracija u zoni povrede uz minimalnu sistemske izloženost [15,16,20].

Posebno su značajni noviji jonski provodni nervni konduiti i hidrogelovi koji omogućavaju istovremenu mehaničku podršku, usmeravanje aksonalnog rasta i kontrolisano oslobađanje litijuma tokom dužeg vremenskog perioda. Ovakve platforme predstavljaju jedan od najvažnijih translacionih pravaca razvoja regenerativne neurologije [19].

U tom kontekstu, posebno mesto zauzima nedavno predstavljena hipoteza "Triple Neuromodulatory Axis". Ovaj koncept integriše tri međusobno komplementarne komponente, litijum, *Hericium erinaceus* i vitamin B12 u jedinstven neuroregenerativni model. Prema ovoj hipotezi, *Hericium erinaceus* primarno stimuliše produkciju neurotrofina, uključujući NGF i BDNF, litijum stabilizuje i pojačava nizvodnu signalizaciju putem inhibicije GSK-3 β i aktivacije CREB-zavisnih mehanizama, dok vitamin B12 obezbeđuje metaboličku i epigenetsku podršku neophodnu za održavanje remijelinizacije i regeneracije aksona. Iako za sada predstavlja teorijski model koji zahteva eksperimentalnu potvrdu, ova hipoteza nudi zanimljiv okvir za razvoj budućih kombinovanih terapijskih strategija zasnovanih na sinergiji farmakoloških, nutritivnih i bioinženjerskih intervencija [23].

Uprkos ohrabrujućim rezultatima, nekoliko važnih ograničenja mora biti uzeto u obzir prilikom interpretacije dostupnih dokaza. Većina studija sprovedena je na glodarima, dok direktni klinički podaci kod pacijenata sa povredama perifernih nerava praktično ne postoje. Dodatno, prisutna je značajna heterogenost u eksperimentalnim modelima, dozama litijuma, dužini terapije i metodama procene regeneracije, što otežava poređenje rezultata između studija. Deo mehaničkih zaključaka zasniva se na istraživanjima centralnog nervnog sistema, koja, iako pružaju značajne uvide u osnovne signalne puteve, ne mogu biti u potpunosti preneti na periferni nervni sistem zbog fundamentalnih razlika u regenerativnom potencijalu i glijalnoj organizaciji [2,12–14,18].

Sveukupno posmatrano, dostupni dokazi podržavaju koncept da litijum predstavlja značajnog farmakološkog kandidata za unapređenje regeneracije perifernih nerava. Njegova sposobnost simultane modulacije neurotrofnih, glijalnih, metaboličkih i inflamatornih procesa razlikuje ga od većine pojedinačnih regenerativnih agenasa. Dalji napredak u razvoju

nervne connections after injury [1]. Although some of these mechanistic insights come from central nervous system models, including the retina and optic nerve [2,18], the basic signaling pathways involved in neuroprotection and axonal growth exhibit a high degree of conservation and are therefore likely to be relevant to the peripheral nervous system as well.

Contemporary research further indicates that the regenerative effects of lithium depend not only on the direct stimulation of cellular growth but also on its ability to regulate cellular homeostasis and energy metabolism. Lithium activates autophagy and promotes the removal of damaged organelles, thereby enhancing the resilience of neurons and Schwann cells during periods of intensive regeneration [12,13]. At the same time, by modulating the PI3K/Akt, ERK1/2, and CREB/BDNF pathways, it contributes to the maintenance of neurotrophic signaling and metabolic stability [10,14]. This integrative effect may explain the regenerative potential of lithium observed across various models of neurological injury.

The particular significance of the analyzed studies is reflected in the shift in research focus in recent years from systemic lithium administration toward local bioengineering-based delivery systems. This approach directly addresses one of the major limitations of lithium's clinical application – its narrow therapeutic window and the potential for renal, endocrine, and neurological toxicity during prolonged systemic exposure [2,16,17]. Lithium-embedded bioadhesives, hydrogels, nanoparticles, and nerve conduits enable the attainment of high local lithium concentrations at the site of injury while minimizing systemic exposure [15,16,20].

Of particular interest are emerging ion-conducting nerve conduits and hydrogels that enable the simultaneous provision of mechanical support, guidance of axonal growth, and controlled release of lithium over an extended period. Such platforms represent one of the most important translational directions in the development of regenerative neurology [19].

In this context, a particular place is occupied by the recently proposed "Triple Neuromodulatory Axis" hypothesis. This concept integrates three mutually complementary components, lithium, *Hericium erinaceus*, and vitamin B12, into a unified neuroregenerative model. According to this hypothesis, *Hericium erinaceus* primarily stimulates the production of neurotrophins, including NGF and BDNF, lithium stabilizes and enhances downstream signaling through inhibition of GSK-3 β and activation of CREB-dependent mechanisms, while vitamin B12 provides the metabolic and epigenetic support necessary to maintain axonal remyelination and regeneration. Although this hypothesis currently rep-

lokalnih sistema isporuke, preciznom definisanju regenerativnih doza i validaciji kombinovanih terapijskih pristupa mogao bi omogućiti prelazak litijuma iz eksperimentalnog okruženja u kliničku praksu regenerativne neurologije.

Pored direktnih eksperimentalnih dokaza o regeneraciji perifernih nerava, pojedini radovi dodatno proširuju translacioni kontekst primene litijuma. Na osnovu toga konstatovano je da litijum pokazuje potencijalne neuroprotektivne efekte i u okviru neurodegenerativnih bolesti, što podrazumeva i Alchajmerovu bolest, pri čemu se njegovo delovanje povezuje sa regulacijom autofagije, neuroinflamacije, oksidativnog stresa i ćelijskog preživljavanja. Iako se radi o drugačijem patofiziološkom okruženju, brojni molekularni putevi identifikovani u neurodegeneraciji preklapaju se sa mehanizmima koji učestvuju u regeneraciji perifernih nerava. Istovremeno, razvoj savremenih biomaterijala otvara nove mogućnosti za lokalnu i kontrolisanu primenu litijuma [24].

U drugoj studiji je pak ustanovljeno da nanohidroksiapatit poseduje povoljne biološke karakteristike za regeneraciju nervnog tkiva i predstavlja potencijalnu platformu za buduće funkcionalizovane sisteme isporuke bioaktivnih molekula [25]. Međutim, sa druge pak strane, konstatovano je da biološki efekti litijuma zavise od koncentracije i dužine trajanja ekspozicije, te da pri neadekvatnim dozama mogu biti u korelaciji sa neurotoksičnim mehanizmima i disbalansom homeostaze ćelija [26]. Ovi rezultati dodatno potvrđuju značaj razvoja preciznih sistema lokalne isporuke i optimizacije doziranja, kako bi se maksimalno iskoristio regenerativni potencijal litijuma uz minimizaciju mogućih neželjenih efekata.

Ograničenja i buduće perspektive

I pored sve većeg broja eksperimentalnih dokaza koji ukazuju na litijum kao potencijalni neuroregulator u regeneraciji perifernih nerava, potrebno je naglasiti nekoliko značajnih ograničenja. Prvo, najveći deo dostupnih podataka potiče iz *in vitro* sistema i životinjskih modela, koji, iako pružaju važan uvid u mehanizme delovanja, ne odražavaju u potpunosti kompleksnost kliničkih stanja kod ljudi, posebno u kontekstu hroničnih lezija, komorbiditeta i heterogenosti povreda. Drugo, značajan deo mehanističkih zaključaka zasniva se na studijama centralnog nervnog sistema, uključujući modele retine, kičmene moždine i ishemijskog oštećenja mozga. Iako ove studije potvrđuju konzerviranost ključnih signalnih puteva (GSK-3 β / β -katenin, PI3K/Akt, ERK1/2), njihova direktna translacija na periferne nerve mora biti interpretirana oprezno zbog fundamentalnih razlika u glijalnoj arhitekturi i regenerativnom potencijalu

represents a theoretical model that requires experimental confirmation, it provides an interesting framework for the development of future combined therapeutic strategies based on the synergy of pharmacological, nutritional, and bioengineering interventions [23].

Despite these encouraging findings, several important limitations should be considered when interpreting the available evidence. Most studies have been conducted on rodents, while direct clinical data from patients with peripheral nerve injuries remain practically nonexistent. Furthermore, considerable heterogeneity exists in experimental designs, lithium doses, treatment duration, and methods used to assess regeneration, making comparisons across studies difficult. Some mechanistic conclusions are based on studies of the central nervous system, which, although providing valuable insights into fundamental signaling pathways, cannot be fully extrapolated to the peripheral nervous system because of fundamental differences in regenerative capacity and glial organization [2,12–14,18].

Taken together, the available evidence supports the concept that lithium represents an important pharmacological candidate for enhancing peripheral nerve regeneration. Its ability to simultaneously modulate neurotrophic, glial, metabolic, and inflammatory processes distinguishes it from most single regenerative agents. Further advances in the development of local delivery systems, precise definition of regenerative doses, and validation of combined therapeutic approaches could facilitate the transition of lithium from the experimental setting to clinical practice in regenerative neurology.

In addition to direct experimental evidence of peripheral nerve regeneration, some papers further broaden the translational context of lithium application. On this basis, lithium has been considered to have potential neuroprotective effects in neurodegenerative diseases, including Alzheimer's disease, where its effects are associated with the regulation of autophagy, neuroinflammation, oxidative stress, and cell survival. Although these represent distinct pathophysiological settings, numerous molecular pathways identified in neurodegeneration overlap with mechanisms involved in peripheral nerve regeneration. At the same time, the development of modern biomaterials opens new possibilities for the local and controlled delivery of lithium [24].

Another study found that nanohydroxyapatite possesses favorable biological characteristics for nerve tissue regeneration and represents a potential platform for future functionalized delivery systems for bioactive molecules [25]. However, it has also been established that the biological effects of lithium depend on

CNS-a i PNS-a. Treće, ne postoji standardizovan terapijski protokol za primenu litijuma u regenerativne svrhe, naročito u kontekstu mikrodoziranja i lokalne isporuke putem biomaterijala, što ograničava uporedivost rezultata između studija. Konačno, klinički dokazi u oblasti povreda perifernih nerava su i dalje oskudni, a većina dostupnih podataka dolazi iz psihijatrijskih ili neurodegenerativnih populacija, a ne iz ciljnih PNS modela.

Buduće istraživanje trebalo bi da bude usmereno ka dobro dizajniranim translacionim studijama koje povezuju prekliničke nalaze sa kliničkom primenom. Poseban fokus treba staviti na razvoj lokalnih bioinženjerskih sistema za isporuku, kao što su hidrogelovi, nervni konduiti i jonski aktivni biomaterijali, koji omogućavaju kontrolisano oslobađanje litijuma direktno u zoni povrede uz minimalizaciju sistemske toksičnosti. Takođe je neophodno precizno definisati odnose doza–efekat u regenerativnom kontekstu, naročito u domenu mikrodoziranja i hormetskih efekata. Na kraju, integrativni terapijski pristupi koji kombinuju litijum sa neurotrofnim i metaboličkim modulacijama predstavljaju obećavajući pravac razvoja sledeće generacije strategija za reparaciju perifernih nerava i funkcionalni oporavak pacijenata.

ZAKLJUČAK

Litijum predstavlja mehanistički utemeljen i eksperimentalno potkrepljen jonski modulator regeneracije perifernih nerava. Dostupni preklinički podaci ukazuju na to da njegovo delovanje obuhvata ključne procese nervne reparacije, uključujući preživljavanje neurona, modulaciju i proliferaciju Švanovih ćelija, aksonalni rast i remijelinizaciju regenerisanih vlakana. Ovi efekti su pre svega posredovani inhibicijom GSK-3 β i aktivacijom nizvodnih signalnih puteva koji uključuju Wnt/ β -katenin, PI3K/Akt i CREB/BDNF osovino, čime se stvara povoljno mikrokruženje za organizovanu regeneraciju nervnog tkiva. Uprkos snažnoj biološkoj osnovi, litijum se ne može posmatrati kao samostalna terapijska strategija, već kao centralni regulatorni element unutar složenih regenerativnih mreža koje uključuju glijalnu podršku, neurotrofne signale i metaboličku stabilizaciju. Njegov puni regenerativni potencijal najverovatnije dolazi do izražaja tek u kombinaciji sa komplementarnim biološkim i inženjerskim pristupima, posebno u okviru lokalnih sistema za kontrolisanu isporuku. Posebno obećavajućim pravcem budućih istraživanja nameće se razvoj multimodalnih terapijskih strategija zasnovanih na konceptu trojne neuromodulatorne ose (litijum–Hericium erinaceus–vitamin B12), koje bi mogle objediniti neurotrofičnu, metaboličku i glijalnu podršku regeneraciji perifernih nerava. Iako su rezultati prekliničkih studija obećavajući, klinička validacija u

the concentration and duration of exposure, and that inadequate doses may be associated with neurotoxic mechanisms and disruption of cellular homeostasis [26]. These findings further underscore the importance of developing precise local delivery systems and optimizing dosing to maximize the regenerative potential of lithium while minimizing potential adverse effects.

Limitations and future perspectives

Despite the growing body of experimental evidence supporting lithium as a potential neuroregulator in peripheral nerve regeneration, several important limitations should be emphasized. First, most of the available evidence come from in vitro systems and animal models, which, although providing important insights into mechanisms of action, do not fully reflect the complexity of human clinical conditions, particularly in the context of chronic lesions, comorbidities, and injury heterogeneity. Second, a substantial proportion of the mechanistic conclusions are based on studies of the central nervous system, including models of retinal, spinal cord, and ischemic brain injury. Although these studies support the conservation of key signaling pathways, including GSK-3 β / β -catenin, PI3K/Akt, and ERK1/2, their direct extrapolation to peripheral nerves should be approached with caution because of fundamental differences in glial architecture and regenerative potential between the CNS and PNS. Third, no standardized therapeutic protocol has been established for the use of lithium for regenerative purposes, particularly with regard to microdosing and local delivery through biomaterials, limiting the comparability of findings across studies. Finally, clinical evidence in the field of peripheral nerve injury remains scarce, with most available data derived from psychiatric or neurodegenerative populations rather than from targeted PNS models.

Future research should focus on well-designed translational studies that bridge preclinical findings and clinical application. Particular attention should be directed toward the development of local bioengineered delivery systems, such as hydrogels, nerve conduits, and ionically active biomaterials, which enable the controlled release of lithium directly at the site of injury while minimizing systemic toxicity. Precise characterization of dose–effect relationships in the regenerative context is also necessary, particularly with regard to microdosing and hormetic effects. Finally, integrative therapeutic approaches combining lithium with neurotrophic and metabolic modulation represent a promising direction for the development of next-generation strategies for peripheral nerve repair and functional recovery in patients.

kontekstu povreda perifernih nerava ostaje ograničena. Na osnovu trenutno dostupnih dokaza, litijum se izdvaja kao jedan od najperspektivnijih farmakoloških modulatora regeneracije perifernih nerava, naročito u kombinaciji sa savremenim sistemima lokalne isporuke i multimodalnim regenerativnim strategijama. Potrebna su dodatna translaciona istraživanja kako bi se definisali optimalni terapijski protokoli, bezbednosni profili i realni funkcionalni ishodi u humanoju populaciji.

Sukob interesa: Nije prijavljen.

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CONCLUSION

Lithium is a mechanistically grounded and experimentally supported ionic modulator of peripheral nerve regeneration. Available preclinical data indicate that its effects involve key processes of nerve repair, including neuronal survival, modulation and proliferation of Schwann cells, axonal growth, and remyelination of regenerated fibers. These effects are primarily mediated through inhibition of GSK-3 β and activation of downstream signaling pathways, including Wnt/ β -catenin, PI3K/Akt, and the CREB/BDNF axis, thereby creating a favorable microenvironment for organized nerve tissue regeneration. Despite its strong biological basis, lithium should not be regarded as an independent therapeutic strategy but rather as a central regulatory element within complex regenerative networks involving glial support, neurotrophic signaling, and metabolic stabilization. Its full regenerative potential is likely to be realized only in combination with complementary biological and engineering approaches, particularly within local controlled-delivery systems. A particularly promising direction for future research is the development of multimodal therapeutic strategies based on the concept of a triple neuromodulatory axis (lithium–*Hericium erinaceus*–vitamin B12), which could integrate neurotrophic, metabolic, and glial support for peripheral nerve regeneration. Although preclinical findings are promising, clinical validation in the context of peripheral nerve injuries remains limited. Based on the currently available evidence, lithium stands out as one of the most promising pharmacological modulators of peripheral nerve regeneration, particularly when combined with modern local delivery systems and multimodal regenerative strategies. Further translational research is needed to define optimal therapeutic protocols, safety profiles, and realistic functional outcomes in human populations.

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