



Therapeutic Potential of Low-Level Laser Therapy in Controlling Inflammation and Damage-Associated Molecular Pattern Regulation in Spinal Cord Injury: A Systematic Review

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Abstract

Introduction: Spinal cord injury (SCI) is a debilitating condition characterized by primary mechanical damage followed by secondary injury processes, including inflammation and gliosis. These complex pathophysiological responses significantly hinder neuronal recovery and functional restoration. Emerging therapies, such as low-level laser therapy (LLLT), offer promising avenues for mitigating these secondary effects and promoting repair. This review aims to explore the pathophysiology of SCI, with a focus on inflammation and gliosis, and to evaluate the therapeutic potential of LLLT in improving outcomes after SCI.

Methods: A comprehensive literature search was conducted across PubMed, Scopus, Cochrane Database, Google Scholar, and Web of Science databases to identify studies published from 2000 to 2024. Keywords included "spinal cord injury," "inflammation," "gliosis," and "low-level laser therapy." Articles were screened based on relevance, and data were extracted and synthesized to provide insights into the mechanisms and therapeutic applications.

Results: Inflammation following SCI involves a cascade of cellular and molecular events that contribute to secondary damage. Gliosis, predominantly driven by astrocytes and microglia, forms a glial scar that impedes axonal regeneration. While these processes are initially protective, their prolonged activation exacerbates neural damage. LLLT has shown the potential to modulate these responses by reducing oxidative stress, promoting anti-inflammatory pathways, and enhancing neuroprotection. Preclinical studies demonstrate that LLLT improves functional recovery, reduces gliosis, and supports axonal regeneration, although standardized protocols and clinical validation remain challenges.

Conclusion: The interplay between inflammation and gliosis significantly influences the outcomes of SCI. LLLT emerges as a promising therapeutic strategy by targeting these processes and promoting regeneration. Further research is needed to standardize LLLT protocols and validate its efficacy in clinical settings, paving the way for improved management of SCI.

Keywords: Spinal cord injury; Inflammation; Gliosis; Low-level laser therapy; Neuroregeneration.



Introduction

Spinal cord injury (SCI) is a devastating condition that results in significant physical, psychological, and socioeconomic burdens worldwide. It disrupts the structural and functional integrity of the spinal cord, leading to motor, sensory, and autonomic impairments.

While the initial mechanical insult constitutes the primary injury, much of the long-term damage arises from secondary injury processes. These processes, which include inflammation and gliosis, exacerbate neuronal loss and hinder repair mechanisms. Inflammation is a hallmark of the secondary phase of SCI and plays a

dual role.¹⁻⁴ In neurodegenerative diseases, free radical production, autophagy, and inflammation are the main factors causing damage to neurons.^{5,6} Closely linked to inflammation is gliosis, a reactive process characterized by astrocyte and glial cell activation. While gliosis forms a protective barrier to prevent the spread of injury, it can also inhibit axonal regeneration and functional recovery.⁷ Recent advances in therapeutic interventions have sought to target these processes to promote healing and improve outcomes in SCI patients.⁸ One promising approach is low-level laser therapy (LLLT), a non-invasive treatment that uses photobiomodulation to modulate cellular functions.⁹ By reducing inflammation and influencing the behavior of reactive glial cells, LLLT has demonstrated the potential to mitigate the detrimental effects of SCI and foster neural repair.¹⁰ This review explores the pathophysiology of SCI with a focus on inflammation and gliosis, highlighting their complex roles in injury progression and recovery. Furthermore, it examines the emerging role of LLLT as a therapeutic strategy, with an emphasis on its mechanisms, preclinical evidence, and future prospects in managing SCI.

Methods

This review article was conducted following established guidelines for systematic and narrative reviews. The process involved a comprehensive literature search, study selection, data extraction, and synthesis to provide a detailed overview of SCI, its pathophysiology, and the therapeutic potential of LLLT.

Search Strategy

A systematic literature search was performed using PubMed, Scopus, Cochrane Database, Google Scholar, and Web of Science databases. The search covered publications up to December 2024 and included both original research articles and review papers. The following keywords and Boolean operators were used: “spinal cord injury” AND (“inflammation” OR “gliosis”) AND “low-level laser therapy”. Additional terms such as “SCI,” “neuroinflammation,” “astrogliosis,” “photobiomodulation,” and “regeneration” were included to refine the search.

The search yielded a total of 326 articles. After removing 51 duplicates, 275 articles remained for title and abstract screening. Of these, 164 articles were excluded based on relevance, leaving 111 full-text articles for further assessment. Following a detailed review, 54 articles met the inclusion criteria and were included in this study (Figure 1).

Eligibility Criteria

Articles were included if they met the following criteria:

- Study type: Original research, systematic reviews, or meta-analyses.

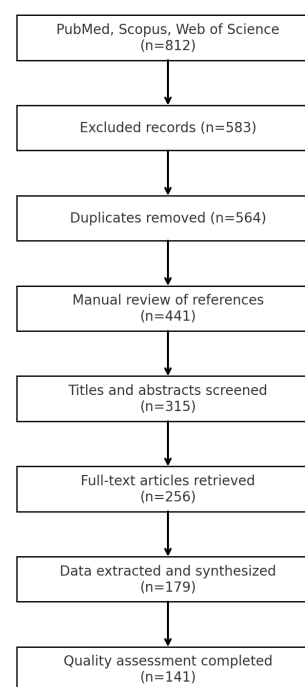


Figure 1. Flowchart of the Systematic Review Search Strategy

- Focus: Studies exploring SCI pathophysiology, including inflammation and gliosis, or evaluating the effects of LLLT.
- Language: Published in English.
- Timeframe: Studies published from 2000 to 2024.
- Human and animal studies: Both preclinical and clinical studies were included.

Exclusion Criteria

- Studies with insufficient details about mechanisms or outcomes related to SCI or LLLT.
- Case reports, editorials, or conference abstracts without full-text access.

Study Selection

All retrieved articles were screened in two phases:

- Title and abstract screening: Initial screening excluded irrelevant articles based on titles and abstracts.
- Full-text review: The remaining articles were reviewed in full to confirm relevance and quality.

Data Extraction

Key data points were extracted from the included studies, including:

- Study design and population characteristics (human or animal models).
- SCI pathophysiological mechanisms, with a focus on inflammation and gliosis.
- LLLT protocols (wavelength, dosage, application timing, and duration).

- Outcomes related to neuroinflammation, neuroprotection, and functional recovery.

Synthesis of Findings

Data from selected studies were synthesized qualitatively to:

- Summarize the underlying mechanisms of SCI, including inflammation and gliosis.
- Highlight the potential therapeutic effects of LLLT.
- Compare and contrast findings across preclinical and clinical studies.

Quality Assessment

The quality of the included studies was assessed using appropriate checklists:

- Preclinical studies: SYRCLE's risk of bias tool.
- Clinical studies: Joanna Briggs Institute (JBI) critical appraisal tools.

Results

SCI involves a complex cascade of pathological events that can be broadly divided into two phases: primary injury and secondary injury. Understanding these phases is critical for developing effective therapeutic interventions.¹¹ The primary injury occurs at the time of trauma and involves immediate mechanical damage to the spinal cord. This includes compression or contusion, shearing forces, hemorrhage, and ischemia. The primary injury is irreversible, initiating a series of events that contribute to secondary injury.¹² Secondary injury is a progressive and prolonged phase that occurs minutes to weeks after the initial trauma. It involves molecular and cellular responses that exacerbate the damage caused by the primary injury. Key components include inflammatory response, oxidative stress, excitotoxicity, edema and vascular dysfunction, cell death, gliosis, and scar formation.¹³ The pathophysiology of SCI reflects a balance between protective and detrimental processes. While some responses, such as inflammation and gliosis, aim to protect and repair the injured tissue, they can also exacerbate damage and limit recovery. Addressing these dual roles is a key challenge in the development of effective therapies.^{11,14}

Inflammation Following SCI

Inflammation is a critical component of the secondary injury phase in SCI. While it plays a role in tissue repair and debris clearance, excessive or prolonged inflammation can exacerbate neuronal damage and impede recovery.¹⁵ Immediately after SCI, the damaged tissue triggers a cascade of inflammatory signals, including the release of damage-associated molecular patterns (DAMPs) from necrotic cells. These DAMPs activate immune cells and initiate the inflammatory response through pattern recognition receptors (PRRs) such as Toll-like receptors

(TLRs). Within hours of injury, neutrophils infiltrate the injury site. They release proteolytic enzymes and reactive oxygen species (ROS) to clear debris but can also damage healthy tissue. Resident immune cells of the central nervous system (CNS) become activated and produce pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α), interleukin-1 beta (IL-1 β), and interleukin-6 (IL-6).^{16,17}

As the injury evolves, monocytes and macrophages migrate to the spinal cord through the compromised blood-spinal cord barrier (BSCB).¹⁸ These cells can adopt distinct phenotypes:

- Pro-inflammatory (M1) macrophages: These cells exacerbate tissue damage by producing inflammatory mediators, ROS, and nitric oxide.¹⁹
- Anti-inflammatory (M2) macrophages: These cells promote tissue repair by secreting growth factors such as transforming growth factor-beta (TGF- β) and brain-derived neurotrophic factor (BDNF).²⁰

The balance between M1 and M2 macrophages is critical for determining the outcome of inflammation.¹⁹

Inflammatory mediators released after SCI orchestrate the immune response^{21,22}:

- Pro-inflammatory cytokines: TNF- α , IL-1 β , and IL-6 contribute to neuronal apoptosis, disruption of the BSCB, and gliosis.
- Anti-inflammatory cytokines: IL-4 and IL-10 counteract inflammation and promote tissue repair.
- Chemokines: Molecules such as CCL2 and CXCL10 attract immune cells to the injury site, amplifying the inflammatory response.

Inflammation in SCI is a complex process with both beneficial and detrimental effects. Beneficial effects include clearing cellular debris and necrotic tissue, promoting angiogenesis and tissue remodeling, and activating repair pathways through anti-inflammatory cytokines and growth factors. Harmful effects are causing secondary neuronal damage via ROS, disrupting axonal integrity and myelin sheaths, and contributing to scar formation and inhibition of axonal regeneration.^{23,24} A deeper understanding of the molecular pathways involved may help in designing therapies that selectively enhance the reparative aspects of inflammation while minimizing its harmful consequences.

Gliosis in SCI

Gliosis is a prominent feature of the secondary injury phase in SCI.²⁵ It is characterized by the activation of glial cells, primarily astrocytes, microglia, and oligodendrocyte precursor cells, in response to injury. Gliosis refers to the reactive response of glial cells to CNS injury.²⁶ Following SCI, glial cells undergo morphological and functional changes, leading to the formation of a glial scar.²⁵ Astrocytes are the primary glial cells involved in gliosis. They undergo hypertrophy and proliferation,

producing a dense network of processes and extracellular matrix (ECM) components. Reactive astrocytes secrete chondroitin sulfate proteoglycans (CSPGs), which inhibit axonal growth, produce cytokines and chemokines that modulate inflammation, and express markers such as glial fibrillary acidic protein (gfap) and vimentin, indicating activation.^{27,28}

The glial scar is a hallmark of chronic gliosis, forming within days to weeks after SCI. It is composed of reactive astrocytes, microglia, oligodendrocyte precursor cells, ECM molecules such as CSPGs, tenascin, and fibronectin²⁹. While the glial scar serves to contain the injury, it also acts as a physical and chemical barrier to axonal regeneration. The scar environment is rich in inhibitory molecules, including CSPGs, which bind to neuronal receptors and block axonal growth. The balance between the pro-inflammatory (M1) and anti-inflammatory (M2) states of microglia determines their overall impact on gliosis.³⁰ Gliosis is an essential but complex process in SCI. While gliosis plays a critical role in containing damage and stabilizing the injury site, its inhibitory effects on regeneration pose a significant barrier to recovery.³¹ Therapeutic strategies that can fine-tune gliosis, enhancing its beneficial aspects while mitigating its harmful effects, hold great promise for improving outcomes in SCI patients.

Low-Level Laser Therapy in SCI

LLLT, also known as photobiomodulation, is an emerging therapeutic approach for managing SCI. By delivering low-intensity, non-thermal light to injured tissue, LLLT stimulates cellular processes that promote repair and recovery.³² LLLT involves the application of light in the red to near-infrared spectrum (600–1100 nm) to the site of injury. The light penetrates tissues and is absorbed by chromophores, particularly cytochrome c oxidase, a key component of the mitochondrial respiratory chain.³³

Key mechanisms include^{34–36} (Table 1):

- **Enhanced cellular energy production:** Absorption of light by cytochrome c oxidase increases mitochondrial activity, leading to elevated ATP production. This provides energy for cellular repair and regeneration.
- **Modulation of ROS:** LLLT reduces excessive ROS levels, preventing oxidative damage while maintaining signaling functions necessary for healing.
- **Regulation of inflammation:** LLLT reduces the production of pro-inflammatory cytokines (e.g., TNF- α , IL-1 β) and increases anti-inflammatory mediators (e.g., IL-10), creating a favorable environment for recovery.
- **Neuroprotection:** LLLT reduces apoptosis in neurons and glial cells by modulating signaling pathways such as the MAPK/ERK and PI3K/Akt pathways.
- **Axonal regeneration:** LLLT promotes axonal sprouting and repair by enhancing the expression of

neurotrophic factors like BDNF and nerve growth factor (NGF).

Studies on animal models and limited clinical trials have demonstrated the potential benefits of LLLT in SCI:

- **Reduction in inflammation:** LLLT suppresses microglial activation and astrocytic gliosis, reducing the inflammatory response.^{37,38}
- **Improvement in functional recovery:** LLLT enhances motor function recovery by promoting neural plasticity and reducing scar tissue formation.^{39–41}
- **Restoration of BSCB:** By modulating vascular responses, LLLT helps restore the integrity of the BSCB, reducing edema and secondary damage.⁴²
- **Promotion of angiogenesis:** LLLT stimulates the formation of new blood vessels, improving oxygen and nutrient delivery to the injured spinal cord.^{32,43}

LLLT can be applied at different stages of SCI and in various settings, and it can reduce inflammation and oxidative stress to prevent secondary damage in the acute phase. Also, it enhances axonal regeneration and functional connectivity in long-term recovery in the chronic phase. Specific protocols, such as wavelength, energy density, and duration of therapy, are optimized based on the stage of injury and the targeted biological effects.^{44–46}

While LLLT holds great promise, there are several challenges. Variability in light parameters (e.g., wavelength, dosage) across studies complicates the comparison of results and clinical translation.⁴⁷ Also, most evidence comes from preclinical studies, with few robust clinical trials conducted to date. Finally, the effectiveness of LLLT in reaching deep spinal cord tissues remains a concern, especially in severe or chronic SCI cases.⁴⁸ LLLT represents a non-invasive, promising approach to addressing the complex pathophysiology of SCI. By modulating inflammation, promoting neuroprotection, and enhancing regeneration, LLLT has the potential to improve outcomes for patients with SCI. However, rigorous clinical research and protocol optimization are essential to integrate LLLT into standard SCI treatment regimens (Table 1).

Discussion

SCI remains a devastating condition with complex pathophysiology, encompassing primary and secondary injury processes.⁵⁷ This review highlights key aspects of SCI, including the inflammatory response, gliosis, and the potential therapeutic application of LLLT. While significant advancements have been made in understanding the mechanisms underlying SCI, effective treatments that address both inflammation and glial scarring while promoting neural regeneration are still lacking. Inflammation is a double-edged sword in SCI recovery. The early inflammatory response involves the activation of microglia and infiltration of peripheral

Table 1. Low-Level Laser Therapy in SCI Studies

Authors	Year	Laser Wavelength	Important Findings
Ando et al ⁴⁹	2013	808-nm	- SCI rats treated with laser irradiation showed significantly higher functional scores. - Locomotive function notably improved from day 10 post-injury in SCI rats treated with laser irradiation aligned parallel to the spinal column, compared to those treated with perpendicular linear polarization.
Paula et al ⁴⁰	2014	780-nm	- Rats with spinal contusion treated with LLLT exhibited faster motor recovery. - LLLT helped maintain urinary system function and preserved nerve tissue at the lesion site. - Treatment showed significant inflammation control and an increase in nerve cells and connections. - LLLT demonstrated positive effects on spinal cord recovery following moderate traumatic SCI.
Veronez et al ⁴⁶	2016	808-nm	- Functional improvements, including enhanced tactile sensitivity, were observed after LLLT at higher fluence levels. - LLLT reduced lesion volume and regulated inflammation by decreasing CD-68 protein expression. - Higher doses of LLLT effectively promoted functional recovery and modulated the inflammatory response.
Janzadeh et al ³⁰	2017	660-nm	- The combination of LLLT and Chondroitinase ABC (ChABC) significantly reduced cavity size and enhanced myelination and axon density around the lesion. - Functional recovery was observed in animals treated with LLLT or ChABC alone, but the combination therapy yielded superior results.
Song et al ⁴¹	2017	810-nm	- LLLT increased the expression of anti-inflammatory cytokines IL-4 and IL-13. - It demonstrated potential in reducing inflammation, modulating macrophage/microglia polarization, and enhancing neuronal survival. - LLLT shows promise as an effective therapeutic option for clinical SCI treatment.
Kim et al ⁵¹	2017	850-nm	- LLLT significantly reduced TNF-α expression at the lesion epicenter and decreased iNOS expression in the caudal segment. - It modulated inflammatory mediators, promoting motor function recovery after SCI. - LLLT applied in the acute phase of SCI holds therapeutic potential for neuroprotection and restoring motor function.
Gong et al ⁵²	2018	810-nm	- Laser treatment inhibited the tissue response to remyelination by suppressing CSPG expression. - It also led to morphological improvements, including reduced glial scar formation and smaller cavity areas.
Mojarad et al ⁴⁵	2018	660-nm	- LLLT resulted in a reduction of neuropathic pain following SCI. - Two weeks of LLLT therapy was more effective in reducing neuropathic pain compared to one week of treatment. - LLLT provided similar pain reduction to Methylprednisolone sodium succinate, without any associated side effects.
Zhang et al ⁵³	2019	810-nm	- LLLT reduced the expression of M1 macrophage-specific markers and increased the expression of M2 macrophage-specific markers. - Forward and reverse experiments confirmed that LLLT activates the PKA-CREB pathway in macrophages, promoting the secretion of neurotrophic factors and stimulating axon regeneration. - Based on these findings, LLLT shows promise as an effective therapeutic approach for SCI, with potential clinical applications.
Poorhassan et al ⁵⁴	2021	810-nm	- Immediate application of PBM (photobiomodulation) treatment after SCI offers neuroprotective effects by controlling oxidative stress and inflammation, preventing further damage. - Photobiomodulation therapy also enhanced functional recovery and reduced cavity formation.
Wang et al ⁵⁵	2021	810-nm	- PBM facilitated motor function recovery, inhibited the activation of neurotoxic microglia and astrocytes, alleviated neuroinflammation and tissue apoptosis, and increased the retention of neurons after SCI. - Lcn2/JAK2-STAT3 crosstalk plays a role in activating neurotoxic microglia and astrocytes after SCI, and PBM can suppress this process.
Neshasteh-riz et al ⁵⁶	2022	660nm	The number of treatment days is crucial for improving mobility, but the daily radiation dose plays a more significant role in pain relief.

immune cells, which play a crucial role in debris clearance and tissue repair. However, prolonged inflammation exacerbates neuronal apoptosis and secondary damage.^{23,24} Similarly, gliosis, primarily mediated by astrocytes and microglia, provides initial protection by stabilizing the injury site and forming a barrier against further damage. Yet, the persistent presence of glial scars, enriched with inhibitory molecules like chondroitin sulfate proteoglycans (CSPGs), inhibits axonal regeneration and functional recovery.^{29,30} Understanding how to balance the beneficial and detrimental effects of inflammation and gliosis is pivotal. Future therapeutic strategies should focus on shifting the inflammatory response from a pro-inflammatory (M1) phenotype to an anti-inflammatory (M2) phenotype, while simultaneously modulating gliosis to preserve its protective roles and mitigate its inhibitory effects.^{19,30} LLLT offers a promising non-invasive treatment strategy for SCI. By modulating cellular processes at the molecular level, LLLT enhances

mitochondrial activity, reduces oxidative stress, and promotes the release of neurotrophic factors.⁵⁸ These effects collectively support neuronal survival, axonal regeneration, and functional recovery. Moreover, LLLT has demonstrated significant potential in modulating both inflammation and gliosis.⁵⁹ The suppression of pro-inflammatory cytokines and the promotion of anti-inflammatory pathways are critical mechanisms by which LLLT mitigates secondary injury. Additionally, the ability of LLLT to reduce astrocytic hypertrophy and CSPG deposition presents an innovative approach to managing glial scarring. These dual effects make LLLT a compelling therapeutic candidate for addressing the multifaceted challenges of SCI.^{39,40} Current SCI treatments, such as surgical decompression, pharmacological interventions (e.g., methylprednisolone), and experimental strategies like stem cell therapy, focus primarily on either mitigating inflammation or promoting regeneration.⁶⁰⁻⁶² LLLT, however, offers the unique advantage of simultaneously

targeting inflammation, oxidative stress, and glial scarring.⁴⁴⁻⁴⁶ Despite these advantages, the translation of LLLT into clinical practice faces several challenges. The variability in protocols, such as wavelength, energy density, and duration, underscores the need for standardization. Furthermore, the depth of light penetration in human tissues, particularly in severe or chronic SCI cases, limits its efficacy and requires further investigation.^{47,48}

The therapeutic potential of LLLT could be significantly enhanced by combining it with other treatments. For instance:

- **Stem cell therapy:** Combining LLLT with stem cell transplantation could synergistically promote neural regeneration and functional recovery.
- **Pharmacological agents:** Co-administration of LLLT with anti-inflammatory or neuroprotective drugs may amplify its benefits.
- **Advanced imaging techniques:** Real-time monitoring of LLLT effects using advanced imaging modalities could optimize treatment protocols and improve outcomes.

Furthermore, large-scale clinical trials are essential to validate the preclinical findings and establish LLLT as a standard therapeutic option for SCI. Collaborative efforts between researchers, clinicians, and engineers will be crucial in overcoming the technical and logistical barriers associated with LLLT implementation. While preclinical studies have provided robust evidence supporting the efficacy of LLLT, the lack of high-quality clinical trials limits its translation into practice. Additionally, the heterogeneity of SCI patients, in terms of injury severity, timing, and comorbidities, poses challenges in designing standardized treatment protocols. Addressing these limitations through well-designed, multicenter clinical studies will be critical for advancing LLLT as a viable treatment for SCI.

Conclusion

The pathophysiology of SCI is marked by complex interactions between inflammation, gliosis, and neural damage, posing significant challenges to recovery. LLLT emerges as a promising therapeutic approach, offering multi-faceted benefits by modulating inflammation, reducing oxidative stress, and managing glial scarring. While the preclinical evidence is compelling, further research is needed to refine protocols, enhance efficacy, and validate LLLT in clinical settings. By addressing these challenges, LLLT could play a transformative role in the treatment of SCI.

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Competing Interests

The authors declare that there is no conflict of interest.

Ethical Approval

This study is under the support of the Medical Research Ethics Committee at Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1403.219).

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References

1. Abbaszadeh H, Niknazar S, Darabi S, Ahmady Roozbahany N, Noori-Zadeh A, Ghoreishi SK, et al. Stem cell transplantation and functional recovery after spinal cord injury: a systematic review and meta-analysis. *Anat Cell Biol.* 2018;51(3):180-8. doi: [10.5115/acb.2018.51.3.180](https://doi.org/10.5115/acb.2018.51.3.180).
2. Abbaszadeh H, Tiraihi T, Delshad AR, Saghedi Zadeh M, Taheri T. Bone marrow stromal cell transdifferentiation into oligodendrocyte-like cells using triiodothyronine as an inducer with expression of platelet-derived growth factor α as a maturity marker. *Iran Biomed J.* 2013;17(2):62-70. doi: [10.6091/ibj.11162.2013](https://doi.org/10.6091/ibj.11162.2013).
3. Bloom O, Herman PE, Spungen AM. Systemic inflammation in traumatic spinal cord injury. *Exp Neurol.* 2020;325:113143. doi: [10.1016/j.expneurol.2019.113143](https://doi.org/10.1016/j.expneurol.2019.113143).
4. Ahuja CS, Wilson JR, Nori S, Kotter MR, Druschel C, Curt A, et al. Traumatic spinal cord injury. *Nat Rev Dis Primers.* 2017;3:17018. doi: [10.1038/nrdp.2017.18](https://doi.org/10.1038/nrdp.2017.18).
5. Darabi S, Noori-Zadeh A, Rajaei F, Abbaszadeh H, Bakhtiyari S, Ahmady Roozbahany N. SMER28 attenuates dopaminergic toxicity mediated by 6-hydroxydopamine in the rats via modulating oxidative burdens and autophagy-related parameters. *Neurochem Res.* 2018;43(12):2313-23. doi: [10.1007/s11064-018-2652-2](https://doi.org/10.1007/s11064-018-2652-2).
6. Darabi S, Tiraihi T, Noori-Zadeh A, Rajaei F, Darabi L, Abbaszadeh H. Creatine and retinoic acid effects on the induction of autophagy and differentiation of adipose tissue-derived stem cells into GABAergic-like neurons. *J Babol Univ Med Sci.* 2017;19(8):41-9. doi: [10.22088/jbums.19.8.41](https://doi.org/10.22088/jbums.19.8.41). [Persian].
7. Yiu G, He Z. Glial inhibition of CNS axon regeneration. *Nat Rev Neurosci.* 2006;7(8):617-27. doi: [10.1038/nrn1956](https://doi.org/10.1038/nrn1956).
8. Cristante AF, de Barros Filho TE, Marcon RM, Letaif OB, da Rocha ID. Therapeutic approaches for spinal cord injury. *Clinics (Sao Paulo).* 2012;67(10):1219-24. doi: [10.6061/](https://doi.org/10.6061/)

- clinics/2012(10)16.
9. Raspa A, Pugliese R, Maleki M, Gelain F. Recent therapeutic approaches for spinal cord injury. *Biotechnol Bioeng*. 2016;113(2):253-9. doi: [10.1002/bit.25689](https://doi.org/10.1002/bit.25689).
 10. Hashmi JT, Huang YY, Osmani BZ, Sharma SK, Naeser MA, Hamblin MR. Role of low-level laser therapy in neurorehabilitation. *PM R*. 2010;2(12 Suppl 2):S292-305. doi: [10.1016/j.pmrj.2010.10.013](https://doi.org/10.1016/j.pmrj.2010.10.013).
 11. Anjum A, Yazid MD, Fauzi Daud M, Idris J, Ng AM, Selvi Naicker A, et al. Spinal cord injury: pathophysiology, multimolecular interactions, and underlying recovery mechanisms. *Int J Mol Sci*. 2020;21(20):7533. doi: [10.3390/ijms21207533](https://doi.org/10.3390/ijms21207533).
 12. Dumont RJ, Okonkwo DO, Verma S, Hurlbert RJ, Boulos PT, Ellegala DB, et al. Acute spinal cord injury, part I: pathophysiologic mechanisms. *Clin Neuropharmacol*. 2001;24(5):254-64. doi: [10.1097/00002826-200109000-00002](https://doi.org/10.1097/00002826-200109000-00002).
 13. Ahuja CS, Martin AR, Fehlings M. Recent advances in managing a spinal cord injury secondary to trauma. *F1000Res*. 2016;5:F1000 Faculty Rev-1017. doi: [10.12688/f1000research.7586.1](https://doi.org/10.12688/f1000research.7586.1).
 14. Lima R, Monteiro A, Salgado AJ, Monteiro S, Silva NA. Pathophysiology and therapeutic approaches for spinal cord injury. *Int J Mol Sci*. 2022;23(22):13833. doi: [10.3390/ijms232213833](https://doi.org/10.3390/ijms232213833).
 15. Okada S. The pathophysiological role of acute inflammation after spinal cord injury. *Inflamm Regen*. 2016;36:20. doi: [10.1186/s41232-016-0026-1](https://doi.org/10.1186/s41232-016-0026-1).
 16. Gaudet AD, Popovich PG. Extracellular matrix regulation of inflammation in the healthy and injured spinal cord. *Exp Neurol*. 2014;258:24-34. doi: [10.1016/j.expneurol.2013.11.020](https://doi.org/10.1016/j.expneurol.2013.11.020).
 17. Liu X, Zhang Y, Wang Y, Qian T. Inflammatory response to spinal cord injury and its treatment. *World Neurosurg*. 2021;155:19-31. doi: [10.1016/j.wneu.2021.07.148](https://doi.org/10.1016/j.wneu.2021.07.148).
 18. Kumar H, Ropper AE, Lee SH, Han I. Propitious therapeutic modulators to prevent blood-spinal cord barrier disruption in spinal cord injury. *Mol Neurobiol*. 2017;54(5):3578-90. doi: [10.1007/s12035-016-9910-6](https://doi.org/10.1007/s12035-016-9910-6).
 19. Honjoh K, Nakajima H, Hirai T, Watanabe S, Matsumine A. Relationship of inflammatory cytokines from M1-type microglia/macrophages at the injured site and lumbar enlargement with neuropathic pain after spinal cord injury in the CCL21 knockout (plt) mouse. *Front Cell Neurosci*. 2019;13:525. doi: [10.3389/fncel.2019.00525](https://doi.org/10.3389/fncel.2019.00525).
 20. Wang L, Wu JP, He XJ. Butylphthalide has an anti-inflammatory role in spinal cord injury by promoting macrophage/microglia M2 polarization via p38 phosphorylation. *Spine (Phila Pa 1976)*. 2020;45(17):E1066-76. doi: [10.1097/brs.0000000000003503](https://doi.org/10.1097/brs.0000000000003503).
 21. Jones TB, McDaniel EE, Popovich PG. Inflammatory-mediated injury and repair in the traumatically injured spinal cord. *Curr Pharm Des*. 2005;11(10):1223-36. doi: [10.2174/1381612053507468](https://doi.org/10.2174/1381612053507468).
 22. Trivedi A, Olivas AD, Noble-Haeusslein LJ. Inflammation and spinal cord injury: infiltrating leukocytes as determinants of injury and repair processes. *Clin Neurosci Res*. 2006;6(5):283-92. doi: [10.1016/j.cnr.2006.09.007](https://doi.org/10.1016/j.cnr.2006.09.007).
 23. Chan CC. Inflammation: beneficial or detrimental after spinal cord injury? *Recent Pat CNS Drug Discov*. 2008;3(3):189-99. doi: [10.2174/157488908786242434](https://doi.org/10.2174/157488908786242434).
 24. David S, López-Vales R, Wee Yong V. Harmful and beneficial effects of inflammation after spinal cord injury: potential therapeutic implications. *Handb Clin Neurol*. 2012;109:485-502. doi: [10.1016/b978-0-444-52137-8.00030-9](https://doi.org/10.1016/b978-0-444-52137-8.00030-9).
 25. Leal-Filho MB. Spinal cord injury: from inflammation to glial scar. *Surg Neurol Int*. 2011;2:112. doi: [10.4103/2152-7806.83732](https://doi.org/10.4103/2152-7806.83732).
 26. Hampton DW, Rhodes KE, Zhao C, Franklin RJ, Fawcett JW. The responses of oligodendrocyte precursor cells, astrocytes and microglia to a cortical stab injury, in the brain. *Neuroscience*. 2004;127(4):813-20. doi: [10.1016/j.neuroscience.2004.05.028](https://doi.org/10.1016/j.neuroscience.2004.05.028).
 27. Sofroniew MV, Vinters HV. Astrocytes: biology and pathology. *Acta Neuropathol*. 2010;119(1):7-35. doi: [10.1007/s00401-009-0619-8](https://doi.org/10.1007/s00401-009-0619-8).
 28. Pekny M, Nilsson M. Astrocyte activation and reactive gliosis. *Glia*. 2005;50(4):427-34. doi: [10.1002/glia.20207](https://doi.org/10.1002/glia.20207).
 29. Silver J, Miller JH. Regeneration beyond the glial scar. *Nat Rev Neurosci*. 2004;5(2):146-56. doi: [10.1038/nrn1326](https://doi.org/10.1038/nrn1326).
 30. Tran AP, Warren PM, Silver J. New insights into glial scar formation after spinal cord injury. *Cell Tissue Res*. 2022;387(3):319-36. doi: [10.1007/s00441-021-03477-w](https://doi.org/10.1007/s00441-021-03477-w).
 31. Karimi-Abdolrezaee S, Billakanti R. Reactive astrogliosis after spinal cord injury-beneficial and detrimental effects. *Mol Neurobiol*. 2012;46(2):251-64. doi: [10.1007/s12035-012-8287-4](https://doi.org/10.1007/s12035-012-8287-4).
 32. Vafaei-Nezhad S, Pour Hassan M, Noroozian M, Aliaghaei A, Shirazi Tehrani A, Abbaszadeh H, et al. A review of low-level laser therapy for spinal cord injury: challenges and safety. *J Lasers Med Sci*. 2020;11(4):363-8. doi: [10.34172/jlms.2020.59](https://doi.org/10.34172/jlms.2020.59).
 33. Musstaf RA, Jenkins DF, Jha AN. Assessing the impact of low-level laser therapy (LLLT) on biological systems: a review. *Int J Radiat Biol*. 2019;95(2):120-43. doi: [10.1080/09553002.2019.1524944](https://doi.org/10.1080/09553002.2019.1524944).
 34. Tam SY, Tam VC, Ramkumar S, Khaw ML, Law HK, Lee SW. Review on the cellular mechanisms of low-level laser therapy use in oncology. *Front Oncol*. 2020;10:1255. doi: [10.3389/fonc.2020.01255](https://doi.org/10.3389/fonc.2020.01255).
 35. Bjordal JM, Lopes-Martins RA, Joensen J, Iversen VV. The anti-inflammatory mechanism of low-level laser therapy and its relevance for clinical use in physiotherapy. *Phys Ther Rev*. 2010;15(4):286-93. doi: [10.1179/1743288X10Y.0000000001](https://doi.org/10.1179/1743288X10Y.0000000001).
 36. Chow R. Low level laser therapy—mechanism of action: analgesia. In: de Freitas PM, Simões A, eds. *Lasers in Dentistry: Guide for Clinical Practice*. John Wiley & Sons; 2015. p. 34-9. doi: [10.1002/9781118987742.ch6](https://doi.org/10.1002/9781118987742.ch6).
 37. Tsai CM, Chang SF, Li CC, Chang H. Transcranial photobiomodulation (808 nm) attenuates pentylenetetrazole-induced seizures by suppressing hippocampal neuroinflammation, astrogliosis, and microgliosis in peripubertal rats. *Neurophotonics*. 2022;9(1):015006. doi: [10.1117/1.NPh.9.1.015006](https://doi.org/10.1117/1.NPh.9.1.015006).
 38. Yoon SR, Hong N, Lee MY, Ahn JC. Photobiomodulation with a 660-nanometer light-emitting diode promotes cell proliferation in astrocyte culture. *Cells*. 2021;10(7):1664. doi: [10.3390/cells10071664](https://doi.org/10.3390/cells10071664).
 39. Soluki M, Abdolmaleki A, Mahmoudi F, Asadi A, Moazedi M. Effect of low-level laser therapy on neurorehabilitation: a narrative review. *J Laser Appl*. 2022;34(1):011201. doi: [10.2351/7.0000577](https://doi.org/10.2351/7.0000577).
 40. Paula AA, Nicolau RA, Lima Mde O, Salgado MA, Cogo JC. "Low-intensity laser therapy effect on the recovery of traumatic spinal cord injury". *Lasers Med Sci*. 2014;29(6):1849-59. doi: [10.1007/s10103-014-1586-4](https://doi.org/10.1007/s10103-014-1586-4).
 41. Song JW, Li K, Liang ZW, Dai C, Shen XF, Gong YZ, et al. Low-level laser facilitates alternatively activated macrophage/microglia polarization and promotes functional recovery after crush spinal cord injury in rats. *Sci Rep*. 2017;7(1):620. doi: [10.1038/s41598-017-00553-6](https://doi.org/10.1038/s41598-017-00553-6).
 42. Svobodova B, Kloudova A, Ruzicka J, Kajtmánova L, Navrátil

- L, Sedlacek R, et al. The effect of 808nm and 905 nm wavelength light on recovery after spinal cord injury. *Sci Rep*. 2019;9(1):7660. doi: [10.1038/s41598-019-44141-2](https://doi.org/10.1038/s41598-019-44141-2).
43. Lin YY, Lee SY, Cheng YJ. Low-level laser therapy induces melanoma tumor growth by promoting angiogenesis. *Life (Basel)*. 2023;13(2):320. doi: [10.3390/life13020320](https://doi.org/10.3390/life13020320).
44. Ayar Z, Gholami B, Piri SM, Kaveh M, Baigi V, Ghodsi Z, et al. The effect of low-level laser therapy on pathophysiology and locomotor recovery after traumatic spinal cord injuries: a systematic review and meta-analysis. *Lasers Med Sci*. 2022;37(1):61-75. doi: [10.1007/s10103-021-03301-5](https://doi.org/10.1007/s10103-021-03301-5).
45. Mojarad N, Janzadeh A, Yousefifard M, Nasirinezhad F. The role of low-level laser therapy on neuropathic pain relief and interleukin-6 expression following spinal cord injury: an experimental study. *J Chem Neuroanat*. 2018;87:60-70. doi: [10.1016/j.jchemneu.2017.04.005](https://doi.org/10.1016/j.jchemneu.2017.04.005).
46. Veronez S, Assis L, Del Campo P, de Oliveira F, de Castro G, Renno AC, et al. Effects of different fluences of low-level laser therapy in an experimental model of spinal cord injury in rats. *Lasers Med Sci*. 2017;32(2):343-9. doi: [10.1007/s10103-016-2120-7](https://doi.org/10.1007/s10103-016-2120-7).
47. Yang TS, Nguyen LT, Hsiao YC, Pan LC, Chang CJ. Biophotonic effects of low-level laser therapy at different wavelengths for potential wound healing. *Photonics*. 2022;9(8):591. doi: [10.3390/photonics9080591](https://doi.org/10.3390/photonics9080591).
48. Mansouri V, Arjmand B, Rezaei Tavirani M, Razzaghi M, Rostami-Nejad M, Hamdih M. Evaluation of efficacy of low-level laser therapy. *J Lasers Med Sci*. 2020;11(4):369-80. doi: [10.34172/jlms.2020.60](https://doi.org/10.34172/jlms.2020.60).
49. Ando T, Sato S, Kobayashi H, Nawashiro H, Ashida H, Hamblin MR, et al. Low-level laser therapy for spinal cord injury in rats: effects of polarization. *J Biomed Opt*. 2013;18(9):098002. doi: [10.1117/1.Jbo.18.9.098002](https://doi.org/10.1117/1.Jbo.18.9.098002).
50. Janzadeh A, Sarveazad A, Yousefifard M, Dameni S, Sahraneshin Samani F, Mokhtarian K, et al. Combine effect of chondroitinase ABC and low-level laser (660nm) on spinal cord injury model in adult male rats. *Neuropeptides*. 2017;65:90-9. doi: [10.1016/j.npep.2017.06.002](https://doi.org/10.1016/j.npep.2017.06.002).
51. Kim J, Kim EH, Lee K, Kim B, Kim Y, Na SH, et al. Low-level laser irradiation improves motor recovery after contusive spinal cord injury in rats. *Tissue Eng Regen Med*. 2017;14(1):57-64. doi: [10.1007/s13770-016-0003-4](https://doi.org/10.1007/s13770-016-0003-4).
52. Gong Y, Wang S, Liang Z, Wang Z, Zhang X, Li J, et al. Label-free spectral imaging unveils biochemical mechanisms of low-level laser therapy on spinal cord injury. *Cell Physiol Biochem*. 2018;49(3):1127-42. doi: [10.1159/000493295](https://doi.org/10.1159/000493295).
53. Zhang J, Sun J, Zheng Q, Hu X, Wang Z, Liang Z, et al. Low-level laser therapy 810-nm up-regulates macrophage secretion of neurotrophic factors via PKA-CREB and promotes neuronal axon regeneration in vitro. *J Cell Mol Med*. 2020;24(1):476-87. doi: [10.1111/jcmm.14756](https://doi.org/10.1111/jcmm.14756).
54. Poor Hassan M, Abdollahifar MA, Aliaghaei A, Tabeie F, Vafaei-Nezhad S, Norouzian M, et al. Photobiomodulation therapy improved functional recovery and overexpression of interleukins-10 after contusion spinal cord injury in rats. *J Chem Neuroanat*. 2021;117:102010. doi: [10.1016/j.jchemneu.2021.102010](https://doi.org/10.1016/j.jchemneu.2021.102010).
55. Wang X, Li X, Zuo X, Liang Z, Ding T, Li K, et al. Photobiomodulation inhibits the activation of neurotoxic microglia and astrocytes by inhibiting Lcn2/JAK2-STAT3 crosstalk after spinal cord injury in male rats. *J Neuroinflammation*. 2021;18(1):256. doi: [10.1186/s12974-021-02312-x](https://doi.org/10.1186/s12974-021-02312-x).
56. Neshasteh-Riz A, Ramezani F, Kookli K, Moghaddas Fazeli S, Motamed A, Nasirinezhad F, et al. Optimization of the duration and dose of photobiomodulation therapy (660nm laser) for spinal cord injury in rats. *Photobiomodul Photomed Laser Surg*. 2022;40(7):488-98. doi: [10.1089/photob.2022.0012](https://doi.org/10.1089/photob.2022.0012).
57. Vafaei-Nezhad S, Niknazar S, Norouzian M, Abdollahifar MA, Aliaghaei A, Abbaszadeh H. Therapeutics effects of [Pyr1] apelin-13 on rat contusion model of spinal cord injury: an experimental study. *J Chem Neuroanat*. 2021;113:101924. doi: [10.1016/j.jchemneu.2021.101924](https://doi.org/10.1016/j.jchemneu.2021.101924).
58. Huang YY, Nagata K, Tedford CE, McCarthy T, Hamblin MR. Low-level laser therapy (LLLT) reduces oxidative stress in primary cortical neurons in vitro. *J Biophotonics*. 2013;6(10):829-38. doi: [10.1002/jbio.201200157](https://doi.org/10.1002/jbio.201200157).
59. Muniz XC, de Assis AC, de Oliveira BS, Ferreira LF, Bilal M, Iqbal HM, et al. Efficacy of low-level laser therapy in nerve injury repair-a new era in therapeutic agents and regenerative treatments. *Neurol Sci*. 2021;42(10):4029-43. doi: [10.1007/s10072-021-05478-7](https://doi.org/10.1007/s10072-021-05478-7).
60. Thuret S, Moon LD, Gage FH. Therapeutic interventions after spinal cord injury. *Nat Rev Neurosci*. 2006;7(8):628-43. doi: [10.1038/nrn1955](https://doi.org/10.1038/nrn1955).
61. Ashammakhi N, Kim HJ, Ehsanipour A, Bierman RD, Kaarela O, Xue C, et al. Regenerative therapies for spinal cord injury. *Tissue Eng Part B Rev*. 2019;25(6):471-91. doi: [10.1089/ten.TEB.2019.0182](https://doi.org/10.1089/ten.TEB.2019.0182).
62. Assinck P, Duncan GJ, Hilton BJ, Plemel JR, Tetzlaff W. Cell transplantation therapy for spinal cord injury. *Nat Neurosci*. 2017;20(5):637-47. doi: [10.1038/nn.4541](https://doi.org/10.1038/nn.4541).