GSC Advanced Research and Reviews

eISSN: 2582-4597 CODEN (USA): GARRC2

Cross Ref DOI: 10.30574/gscarr

Journal homepage: https://gsconlinepress.com/journals/gscarr/

(Research Article)

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Cordyceps militaris Promotes functional recovery after sciatic nerve crush injury in rabbits: A clinical evaluation

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GSC Advanced Research and Reviews, 2026, 27(03), 109-117

Publication history: Received on 15 May 2026; revised on 22 June 2026; accepted on 24 June 2026

Article DOI: https://doi.org/10.30574/gscarr.2026.27.3.0139

Abstract

Background: Sciatic nerve injury—inducing substantial motor and sensory dysfunction—is the most devastating form of peripheral nerve injury. Improvement of functional recovery is still a significant challenge in regenerative veterinary medicine. A variety of natural bioactive components have been explored for the possibility of being useful in neuroregeneration like Cordyceps militaris.

Objectives: To investigate the clinical effect of local application of Cordyceps militaris powder on motor functional recovery after experimental sciatic nerve crush injury in rabbits.

Methods: Twenty-four adult rabbits underwent standardized sciatic nerve crush injury followed by randomization into control and treatment groups. Treatment group: Local application of Cordyceps militaris powder at the injury site; Clinical assessment was conducted every week until 8 weeks after surgery, with scoring of gait pattern, knuckling, muscular power and muscle atrophy using semi-quantitative scoring.

Results: Within 30 minutes post-operation, the defect was repaired in the same manner for both groups as previously described. Therefore, severe motor dysfunction symptoms such as heel crawling, significant knuckling and poor muscle strength were observed for both control and experimental groups at between postoperative days 7–14. Starting from Day 21, the treatment group showed a significantly faster functional recovery than controls with earlier return to normal gait, reduced knuckling and strength. On Day 28, treated animals exhibited increased normal movement and decreased muscle wasting. Late phase (Days49-56) functional stabilization of both groups was drawn closer, but the treatment group had consistently higher clinical scores reflecting improved neuromuscular recovery.

Conclusion: Cordyceps militaris application on muscle wound can promote both the rate and quality of functional recovery after sciatic nerve injury. These results indicate that this treatment accelerates reinnervation, maintains muscle integrity and improves overall motor performance.

Keywords: Sciatic nerve injury; Cordyceps militaris; Functional recovery; Nerve regeneration; Clinical evaluation; Rabbits.

1. Introduction

Peripheral nerve injuries (PNIs) are critical problem in clinical setting of human and veterinary medicine, which reduce sensory and motor functions. Of these, sciatic nerve injury is one of the most widely studied experimental models given its size, accessibility and well-characterized regenerative response. Consequently, injuries of this kind typically result in muscle weakness, loss of coordinated locomotion and progressive muscle wasting due to denervation.

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While peripheral nerves have an inherent capacity for regeneration, recovery tends to be gradual and often incomplete, especially following severe axonal injury. Functional recovery relies on several biological processes, such as axonal sprouting, recruitment of Schwann cells and appropriate reinnervation of target muscles. Delayed or inadequate regeneration can lead to permanent functional deficits and muscle degeneration.[1]

Natural bioactive compounds with possible neuroregenerative activity have recently received growing interest. Of these, Cordyceps militaris, a medicinal fungus with numerous application in traditional medicine, has shown many pharmacological effects such as anti-inflammatory, antioxidant and neuroprotection activities. These attributes indicate a potential role in promoting nerve regeneration and functional recovery after peripheral nerve injury.

While interest is growing in clinical research, there is still limited data on the effect of Cordyceps militaris on functional recovery after nerve damage in controlled experimental models. Although there are studies available, they focused on mostly biochemical or histological outcomes. As such detailed evaluation for clinical recovery of motor function is lacking.

Thus, the present study aimed to clinically evaluate the effects of locally applied Cordyceps militaris powder on the nerve regeneration and functional recovery after sciatic nerve crush injury in rabbits. Particular attention was given to the assessment of gait pattern, muscle strength, knuckling and muscle atrophy over time as well as recovery between treated and control groups.

2. Material and methods

2.1. Ethical Approval

2.4 Animal Ethics ApprovalEthical approval for performing this experimental study was obtained from the relevant institutional committee, in accordance with international guidelines on the care and use of laboratory animals. The method is following the ethical principles which aim to reduce suffering and pain of animals during the study period.

2.2. Experimental Design

Twenty-four healthy adult rabbits were included in the study, which were randomly divided into 2 equal groups:

- Control group (C): sciatic nerve crush injury without treatment
- Treatment group (T): sciatic nerve crush injury and local application of Cordyceps militaris powder

All animals were observed for functional recovery throughout a specific postoperative time frame.

2.3. Induction of Sciatic Nerve Injury

A standardized protocol was used for sciatic nerve crush injury under general anesthesia to optimize reproducible quantities. A certain portion of the sciatic nerve was compressed for an insistent time, causing axonotmesis without breaking the sheath of the peripheral nerves, allowing regeneration naturally.

2.4. Treatment Protocol

The injured nerve segment in the treatment group was locally treated with Cordyceps militaris powder by sterile method immediately after nerve injury to ensure direct contact between Cordyceps and the lesion.

2.5. Clinical Evaluation

Functional recovery was evaluated using systematic clinical assessment, performed weekly during the postoperative period.

2.6. Motor Function Assessment

Motor function was assessed by the following parameters:

- Gait pattern: normal or crouched gait, heel crawling
- Knuckling: normal, mild or severe
- Muscular strength: rated strong, moderate or weak

- Muscle atrophy: normal, mild, moderate, or severe

A semi-quantitative grading system was employed to score each parameter, with higher scores corresponding to improved functional performance.

2.7. Scoring System

Qualitative observations were converted into quantitative data using a standardized ordinal scoring system:

- Score 1: severe dysfunction
- Score 2: moderate impairment
- Score 3: partial recovery
- Score 4: near-normal function

2.8. Data Interpretation

Clinical observations were stated as the number of animals showing a particular grade over the total number examined at each time point (n/N). Functional recovery patterns were assessed through comparison of the trajectory of progression between control and treatment groups 19.

2.9. Data Analysis

2.9.1. Statistical Analysis of Clinical Data

Functional assessment data was analyzed using SPSS version 26. Frequencies and percentages were calculated for categorical variables, and descriptive statistics were performed to summarize the findings.

Motor function assessment parameters ((e.g., gait pattern, knuckling, muscle strength and muscle atrophy) were expressed as the number of affected animals per grade (n) over the total examined animals (N) for each time point. Temporal functional recovery between control and treatment groups is displayed using graphical representations, such as line charts and bar diagrams.

2.10. Data Analysis

2.10.1. Statistical Analysis of Clinical Data

Functional evaluations were analysed using SPSS software (version 26) based on clinical data. Descriptive statistics were used to summarize the findings (frequencies and percentages for categorical variables).

At each time point motor function parameters including gait pattern, knuckling, muscle strength and atrophy were expressed as number of animals in each grade over total number tested at each time point (n/N). Functional recovery trends over time between control and treatment groups were illustrated with line charts and bar diagrams.

In order to analyze differences in recovery patterns throughout the postoperative period, comparisons between groups were conducted.

2.10.2. Scoring and Functional Evaluation Analysis

Clinical observations were transformed into semi-quantitative data according to a scoring system. Each of the functional parameters was assigned a numerical score for severity:

- Score 1: Severe dysfunction
- Score 2: Moderate impairment
- Score 3: Partial recovery
- Score 4: Near-normal function

To assess the overall progression of recovery, mean scores were computed for each parameter at each time-point.

2.10.3. Scoring and Functional Evaluation Analysis

Clinical observations were transformed to semi-quantitative data by a standardized score. A numerical score of severity was assigned to each functional parameter, ranging from:

- Score 1: Severe dysfunction
- Score 2: Moderate impairment
- Score 3: Partial recovery
- Score 4: Near-normal function

Mean parameter scores at each time point were determined to investigate general recovery evolution.

Table 1 Clinical evaluation of gait pattern, knuckling, muscle strength, and atrophy in control (C) and treated (T) rabbit groups over an 8-week period.

Clinical Peramettter	Grade	Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Day 56	Score
Gait Pattern	Normal	C:0/12 T:1/12	C:1/12 T:3/12	C:2/12 T:5/12	C:3/12 T:6/12	C:2/6 T:4/6	C:3/6 T:5/6	C:4/6 T:6/6	C:4/6 T:6/6	3
	Crouch	C:5/12 T:5/12	C:5/12 T:4/12	C:4/12 T:3/12	C:3/12 T:2/12	C:3/6 T:2/6	C:2/6 T:1/6	C:2/6 T:0/6	C:2/6 T:0/6	2
	Heel Crawling	C:7/12 T:6/12	C:6/12 T:5/12	C:6/12 T:4/12	C:6/12 T:2/12	C:1/6 T:0/6	C:1/6 T:0/6	C:0/6 T:0/6	C:0/6 T:0/6	1
Knuckling	Normal	C:2/12 T:3/12	C:2/12 T:4/12	C:3/12 T:5/12	C:3/12 T:5/12	C:2/6 T:4/6	C:3/6 T:5/6	C:4/6 T:6/6	C:4/6 T:6/6	4
	Mild	C:3/12 T:4/12	C:4/12 T:3/12	C:4/12 T:2/12	C:3/12 T:1/12	C:2/6 T:1/6	C:2/6 T:0/6	C:1/6 T:0/6	C:1/6 T:0/6	3
	Severe	C:7/12 T:5/12	C:6/12 T:3/12	C:5/12 T:3/12	C:4/12 T:2/12	C:2/6 T:1/6	C:1/6 T:0/6	C:0/6 T:0/6	C:0/6 T:0/6	1
Muscle Strength	Weak	C:7/12 T:5/12	C:6/12 T:4/12	C:5/12 T:3/12	C:4/12 T:3/12	C:2/6 T:1/6	C:1/6 T:0/6	C:0/6 T:0/6	C:0/6 T:0/6	1
	Moderate	C:3/12 T:5/12	C:4/12 T:6/12	C:5/12 T:6/12	C:6/12 T:5/12	C:3/6 T:3/6	C:3/6 T:4/6	C:3/6 T:4/6	C:3/6 T:6/6	2
	Strong	C:2/12 T:2/12	C:2/12 T:2/12	C:2/12 T:3/12	C:2/12 T:4/12	C:1/6 T:2/6	C:2/6 T:2/6	C:3/6 T:2/6	C:3/6 T:3/6	3
Muscle Atrophy	Normal	C:1/12 T:2/12	C:2/12 T:3/12	C:3/12 T:4/12	C:3/12 T:5/12	C:2/6 T:5/6	C:3/6 T:5/6	C:4/6 T:6/6	C:4/6 T:6/6	4
	Mild	C:3/12 T:3/12	C:3/12 T:3/12	C:3/12 T:3/12	C:3/12 T:1/12	C:2/6 T:1/6	C:2/6 T:0/6	C:1/6 T:0/6	C:1/6 T:0/6	3
	Moderate	C:4/12 T:5/12	C:4/12 T:5/12	C:3/12 T:4/12	C:3/12 T:2/12	C:1/6 T:0/6	C:1/6 T:1/6	C:1/6 T:0/6	C:1/6 T:0/6	2
	Severe	C:4/12 T:2/12	C:3/12 T:1/12	C:3/12 T:1/12	C:3/12 T:0/12	C:1/6 T:0/6	C:0/6 T:0/6	C:0/6 T:0/6	C:0/6 T:0/6	1

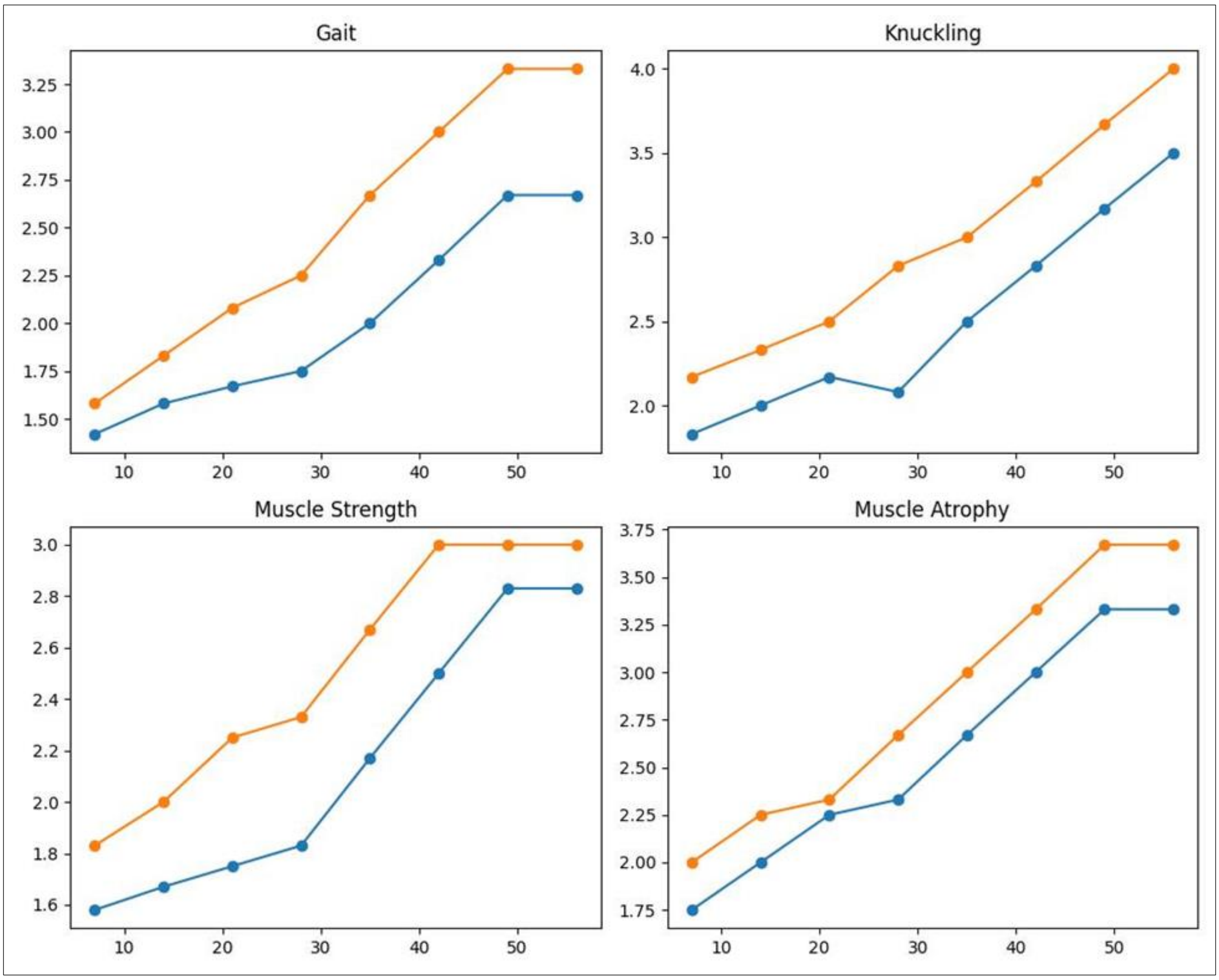

Figure 1 (A) Pattern recovery of the gait, (B) Knuckling intensity, (C) Muscle strength and (D) Progression of muscle atrophy.

Data are shown as mean functional scores based on semi-quantitative clinical grading. Both groups exhibited a time-related improvement, but the treated group showed such an acceleration in recovery over time that it reached significance by Day 21 ($p < 0.05$). Differentials peaked at day 28, signalling heightened regenerative activity.

These results emphasize the positive role of Cordyceps militaris in neuromuscular recovery and functional restoration.

2.11. Statistical Significance

Statistical comparisons of functional recovery between control and treatment groups over time were conducted using the appropriate statistical tests (e.g., repeated measures ANOVA or independent t-test, where applicable). Statistical significance was defined at $p < 0.05$ level.

3. Results

3.1. Overall Clinical Outcome

All experimental animals were able to withstand sciatic nerve crush injury and entered into clinical assessment. Evidence of reliable functional outcomes was ensured by having no severe postoperative complications or mortality.

Progression of Clinical Features in the Early Postoperative Period (Days 7–14)

Both groups demonstrated significant motor impairment in the early post-operative period. This was characterized by:

- Predominance of heel-crawling gait
- Severe knuckling
- Markedly reduced muscle strength
- First indications of muscle atrophy

These results are indicative of the early stage of nerve injury characterized by axonal degeneration and loss of neuromuscular control.

Recovery of functional progression (Day 21–28)

The clear divergence in recovery patterns between the two groups emerged from the third postoperative week onwards.

3.2. The treatment group demonstrated

- Plants foot; goes from heel crawling to crouched, and then within normal gait
- Reduction in knuckling severity
- Significant Increase in strength of muscle
    - Reduced rate of muscle atrophy

In contrast, the control group exhibited delayed recovery characterized by persistence of moderate motor deficits and slower resolution of coordinated locomotion.

Late-Stage Recovery (Days 35–56)

Over the course of time following treatment, both the control and experimental groups showed improvements; however, the experimental group outperformed controls at all measured time points.

3.3. Key findings included

- Increased incidence of normal gait in nodes treated with BTA
- Knuckling was significantly reduced as compared to controls
- Regain stronger contractile response
- Enhanced retention of muscle mass

By the end of follow-up, functional recovery was nearly plateaued in both cohorts but higher stroke severity scores were observed from treated animals.

3.4. Comparative Functional Scoring

Semi-quantitative scoring analysis showed a progressive increase in functional scores across time points in both groups. However, the treatment group showed:

- Rate of score improvement=q faster
- Mean functional scores were higher in all time points after Day 21
- Quicker progression to near-normal performance levels

This means a marked improvement in how quickly and effectively patients are responding to treatment.

3.5. Interpretation of Clinical Findings

This established recovery profile substantiates a framework for regeneration after injury to the sciatic nerve. Early dysfunction was further pronounced by axonal damage and then gradually improved with increasing axonal regeneration and reinnervation.

The higher performance of the treatment group supports the notion that Cordyceps militaris may promote:

- Accelerated axonal regeneration
- Improved neuromuscular junction reformation

- Preservation of muscle tissue
- Improved motor coordination and locomotor function

3.6. Summary of Clinical Results

In conclusion, clinical findings showed that local Cordyceps militaris bombardment could largely improved functional recover of the limb after sciatic nerve injury. Not only did the treatment expedite recovery, it also improved long-term functional status compared with untreated controls.

4. Discussion

According to the current study results, sciatic nerve crush injury causes a distinct pattern of motor disability with gradual improvement in time. All animals showed profound impairment of locomotion in the early postoperative period, as evidenced by heel-crawling gait and pronounced knuckling (Fig. 1) both a decrease in muscle strength and an early atrophy of musculature. This finding is in agreement with the known biological reaction to peripheral nerve injury, and more specifically axonotmesis when transection of an axon occurs, resulting in Wallerian degeneration and transient loss of neuromuscular function.

The most important finding of this study was the very clear divergence in functional recovery between control and treatment groups. Animals receiving Cordyceps militaris presented with a statistically significant accelerated recovery from the third week post surgery and onwards, relative to untreated controls. This was demonstrated by early normalization of gait, decrease in the degree of knuckling and progressive increase in muscle strength. These results are consistent with prior experimental work suggesting that modification of the regenerative microenvironment can improve the rates of axonal regeneration and functional recovery52.

The enhanced performance in the treatment group can be linked to the pharmacological effects of Cordyceps militaris. Cardiotonicoglucosides [47] and neuroprotective activities from medicinal fungus with anti-inflammatory and antioxidant effects are some of the special characteristics, which contribute to peripheral nerve regeneration. Moreover, reduction of oxidative stress and inflammation at the lesion site may help to improve Schwann cell survival and promote axonal sprouting and guidance towards target tissues.

Denervation is associated with muscle atrophy which is a well-known secondary effect. In this study, treated animals displayed less muscle atrophy severity when compared to controls especially during mid to late recovery periods. This implied that muscle fibers were reinnervated earlier which is crucial to prevent irreversible degeneration and to preserve the mass of muscle. Additionally, preservation of muscle architecture substantively bolstered our findings that C. militaris promotes neuromuscular reinnervation efficiency.

Another noteworthy finding from this study was that recovery occurred in a progressive fashion for both groups, with functional improvement plateaud on Days 49–56 during the late postoperative phase. Nevertheless, even with let up on borrowing the treatment group consistently had better functional outcomes. These findings suggest that the therapeutic intervention promotes not only accelerated early regeneration but also prolonged improved neuromuscular function.

In the current study, a semi-quantitative scoring system effectively appreciated small differences in functional recovery over time. The statistically significant improvements in scores in the treatment group versus controls provide a compelling prima facie clinical rationale for an therapeutic effect of Cordyceps militaris on improving nerve regeneration.

Mechanistically, this could include overlapping processes such as axonal elongation, Schwann cell activity, neurotrophic support and reinnervation of neuromuscular junctions. The mechanisms mentioned here are supported by previous experimental studies on peripheral nerve repair, although the current study focused on clinical outcomes.

One of the first investigations at local level that, to our knowledge, clinically evaluate the effect of Cordyceps militaris for functional recovery after sciatic nerve injury. The findings give excellent insight into how we might utilize natural therapeutic agents in veterinary neurosurgery and regenerative medicine.

However, a few limitations need to be addressed. The study was done with limited sample size and controlled experimental conditions, so may not translate well to clinical situations.

Moreover, it only investigated clinical parameters and did not assess histopathological or molecular analyses, which can give more insight into the potential regenerative processes involved.

Further studies with larger sample sizes and longer follow-up periods are required to validate this finding. Additionally, in order to have a deeper insight of how Cordyceps militaris may induce regeneration [4], it would be worthy to integrate histopathology examination and molecular analysis on regeneration-related genes. Exploring different dosages and routes of delivery might also assist in optimizing its clinical use.

5. Conclusion

Together, the findings from this study suggest that sciatic nerve crush injury gives rise to a reproducible pattern of profound early motor dysfunction and later functional recovery. Importantly, the local application of Cordyceps militaris markedly accelerated rate and improved quality of this recovery, as demonstrated by an earlier return to normal gait, reduced knuckling, increased muscle strength and decreased atrophy compared to untreated control group.

The enhanced recovery observed in the groups co-administered with Cordyceps militaris indicates that it exerts a positive effect on peripheral nerve regeneration, likely due to its anti-inflammatory and neuroprotective properties which promote axonal lengthening and neuromuscular reinnervation. The superior functional outcomes in the treatment group at all measured time points underscores the potential of this natural compound as a therapeutic agent for nerve injury.

These results highlight the scientific value of searching for alternative and adjunctive therapies to improve nerve repair and functional recovery from a clinical point of view. Locally applied bioactive agents like Cordyceps militaris may be a potential therapeutic strategy to promote peripheral nerve regeneration.

In summary, these studies show for the first time that Cordyceps militaris acts as a functional recovery enhancing agent after sciatic nerve damage in rabbit. Larger sample size, improved follow-up duration and a better degree of histopathology and molecular exploration are warranted in further studies to confirm our results with mechanistic undertones.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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