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Aqueous cinnamomum extract (Cinnamomum zeylanicum) improves sciatic nerve regeneration after injury in rats

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SUMMARY

Peripheral nerve damage represents a prevalent medical concern, often precipitated by trauma, tumors, and damage resulting from medical interventions. These factors instigate biochemical and inflammatory changes at the injury site, exacerbating nerve degeneration. Consequently, mitigating these alterations may facilitate nerve protection post-injury. The present study aimed to assess the potential enhancement of the nerve regeneration process and improved functional outcomes by administering cinnamon aqueous extract (CAE) after sciatic nerve crush in rats. A total of 28 rats were allocated into four groups: sham, injury, and CAE at dosages of 100 and 400 mg/kg/day. By forceps, a crush injury was inflicted on the sciatic nerve on the left side.

Following this, CAE was managed for 28 consecutive days. Weekly assessments were conducted to measure the sciatic functional index (SFI). Additional evaluations involved electrophysiological and histomorphometric analyses, gastrocnemius muscle wet weight measurements, and serum total oxidant status (TOS) assessments. The results indicated that CAE could expedite recovery of the sciatic nerve following crush injury, with the 400 mg/kg/day dosage demonstrating superior effects on SFI recovery, muscle mass ratio, and myelin content.

This study illustrates that CAE exerts a beneficial influence on peripheral nerve restoration. Therefore, CAE therapy may be a promising treatment modality for peripheral nerve regeneration and functional recovery. However, further investigations are necessary to validate these findings and determine the optimal dosage of CAE.

Key words: Cinnamon – Crush – Nerve injury – Rat – Regeneration

INTRODUCTION

Peripheral nerve injury (PNI) is a prevalent clinical issue that arises from various factors, including traumatic events. Consequently, a significant number of individuals experience such injuries with an estimated incidence of 11.2 per 100,000 population annually in England (Murphy et al., 2023) and 36.9 per 1,000,000 person-years in the United States for sports and recreation-related injuries (Li et al., 2020). These injuries are asso-

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ciated with numerous complications, including substantial disability, diminished quality of life, and considerable economic burdens (Murphy et al., 2023b). The etiological factors contributing to the affected lesions are highly heterogeneous, encompassing conditions such as elongation, transection, laceration, and compression (Zaidman et al., 2024). Traumatic causes account for a large proportion of PNIs, with vehicular accidents being the most common etiology (46.4-54.6%), followed by penetrating injuries (23.9%) (Kouyoumdjian et al., 2017; Aman et al., 2022). It predominantly affects males and upper limb nerves (Murphy et al., 2023; Li et al., 2020).

Additional factors that may contribute to the damage of peripheral nerves include a variety of metabolic disorders, like diabetic neuropathy affecting 50% of type 2 diabetes patients, and neurotoxic exposures, particularly chemotherapy-induced neuropathy occurring in 68% of treated patients after a few months. These factors can have a profound effect on nerve function and overall health, potentially resulting in a spectrum of neurological disorders (Gibbons 2020; Hicks and Selvin, 2019; Desai et al., 2022; Seretny et al., 2014).

Thus, any mismanagement or inappropriate intervention may lead to the loss of sensory, motor, and autonomic functions (Yüce et al., 2015). Around 24 to 48 hours following neuronal damage, Wallerian degeneration commences, initiating a cascade of cellular and molecular alterations.

This procedure triggers inflammatory and biochemical responses, leading to dorsal root ganglia death (DRGs), extensive cellular migration and proliferation, neuronal loss in the spinal cord, and apoptosis. These events subsequently result in the generation of free radicals, the formation and increase of toxic materials, and the development of scar tissue, all of which impede axonal regeneration and recovery (Houschyar et al., 2016; Faroni et al., 2015). Despite notable advancements in the understanding of the pathophysiology of peripheral nerve injury and repair, as well as empirical investigations aimed at mitigating the consequences of neural damage, the recovery and regeneration of neural tissues continue to pose significant challenges (Houschyar et al., 2016; Yüce et al., 2015).

Although there is a lack of effective medical therapies for the regeneration of peripheral nerve injuries, clinical interventions for nerve repair remain essential (Murphy et al., 2023; Feng and Yuan, 2015). Wallerian degeneration encompasses the breakdown of myelin and the movement of Schwann cells (SCs) and macrophages to the site of degeneration in the nerve fibers, facilitating the clearance of nerve debris. Furthermore, during Wallerian degeneration, various free radicals and pro-inflammatory cytokines, such as tumor necrosis factor α (TNF-α), interleukin-1 beta (IL-1ß), and interleukin-6 (IL-6), are released by phagocytic cells, including macrophages and SCs (Ma and Eisenach, 2003; Rock and Kono, 2008). Consequently, the regulated release of inflammatory and oxidative mediators can represent a hopeful therapeutic strategy for nerve repair via mitigating scar tissue formation (Ma and Eisenach, 2003; Atik et al., 2011). Numerous researchers have investigated the beneficial effects of exogenous mediators on nerve repair, suggesting that certain exogenous compounds that modulate inflammatory mediators and free radical production can enhance nerve regeneration and remyelination (Izhiman and Esfandiari, 2024; Li et al., 2020; Moharrami Kasmaie et al., 2019; Kocaoglu et al., 2017). The current investigation is directed towards novel exogenous agents that may offer greater efficacy and reduce undesirable consequences on nerve regeneration. Cinnamon, the most recognized spice derived from Cinnamomum trees, has been shown to possess a range of therapeutic properties, including antioxidant, anti-tumor, anti-inflammatory, and neuroprotective effects (Roghani et al., 2017; Ho et al., 2013; Patra et al., 2012; Chen et al., 2016). This herb contains various bioactive compounds that exhibit strong anti-inflammatory and antioxidant properties (Davoudi and Ramazani, 2024; Stavinoha and Vattem, 2015; Ho et al., 2013).

Research indicates that cinnamon significantly inhibits the production and creation of numerous inflammatory factors and free radicals, suggesting its potential neuroprotective role in neurodegenerative conditions following nerve damage.

Researchers propose that cinnamon may be a therapeutic agent for neurodegenerative disorders within the central nervous system (Liu et al., 2017; Roghani et al., 2017; Pyo et al., 2013). Considering the previously mentioned benefits of cinnamon, mainly its ability to modulate inflammation in the nervous system and its encouraging effects on nervous tissue repair, the current study aims to investigate the role of cinnamon in regenerating peripheral nerves using a rat crush injury model.

MATERIALS AND METHODS

Cinnamon extract preparation

The dried bark of Cinnamomum zeylanicum (CZ) was sourced from a local retailer and authenticated by the Department of Pharmacognosy at Guilan University, assigned Herbarium number GUMS-C17. The bark was ground into a coarse powder, and an aqueous extract was prepared by soaking 100 grams of the material in 300 milliliters of distilled water at 35°C for 24,

48, and 72 hours. The extract was filtered (GE Healthcare, UK), concentrated with a rotary evaporator (Heidolph, Germany), and freeze-dried (Christ, Germany), resulting in a dark brown powder stored at -20°C.

Cinnamon extract analysis

The aqueous extract of cinnamon was analyzed via gas chromatography coupled with mass spectrometry (GC/MS, Agilent 7890A, USA) to identify its active constituents. This analysis was conducted at Varna Paya Pajooh Maham, a private biotechnology laboratory in Rasht, Iran.

Experimental and animal groups

The study involved twenty-eight male Wistar rats, each weighing between 250 and 300 grams and aged 8 to 10 weeks, all exhibiting normal motor function as indicated by an SFI score of approximately 0. The animal care and research protocols were approved by the Ethics Committee of Guilan University of Medical Sciences (license number: IR.GUMS.REC.1397.154,2018). The rats were housed in autoclavable Makrolon polycarbonate cages (dimensions: 42 x 27 x 15 cm; Tajhiz Gostar, Iran), with continuous access to food and water, under controlled environmental conditions characterized by a humidity level of 55% ± 5% and a 12-hour light-dark cycle, maintained at a room temperature ranging from 18°C to 21°C. Following a two-week acclimatization period, the animals were randomly assigned to four groups (n=7 each): Sham (control), clamp (injury), clamp + CAE (100 mg/kg/day), and clamp + CAE (400 mg/kg/day), hereafter referred to as CAE100 and CAE400, respectively. The two experimental groups received cinnamon extract orally at 100 mg/kg and 400 mg/kg via syringe (Ranasinghe et al., 2012). The animals were administered the extract four weeks post-surgery through syringe feeding.

Surgical procedures

Sedation was induced through intraperitoneal (IP) administration of xylazine (10 mg/kg, Interchemie, Holland) and ketamine (100 mg/kg, Rotexmedica, Germany). Following sedation, the rats were prepared for surgery, and the surgical site was first disinfected using a 10% povidone-iodine solution. Following this, the hair in the area was shaved, and the site was subsequently disinfected once more with the solution. A 2 cm incision was made in the fascia and skin of the posterior left thigh. Subsequently, the biceps femoris and vastus lateralis muscles were meticulously dissected to expose the sciatic nerve. In a controlled experimental procedure, the sciatic nerve, 1 cm proximal to its bifurcation, was subjected to a crush injury. The injury was inflicted by a clamp for two minutes. Post-operative care involved monitoring the animals as they recovered from sedation under a heat lamp, after which they were allowed to access food and water ad libitum. To reduce the risk of infection, a subcutaneous injection of 0.1 cc of enrofloxacin 5% was administered for three days postoperatively. Syringe feeding commenced the day following the surgery and continued for 28 consecutive days —a single trained individual conducted all surgical procedures before noon.

Functional recovery assessment

The Sciatic Functional Index (SFI) was evaluat-

ed on postoperative days 7, 14, 21, and 28. In this experimental setup, the hind paws of the subjects were marked with black ink, and the rats were subsequently allowed to traverse a designated track measuring 50 × 7.5 cm^2. Following this, the SFI of the sciatic nerve was determined by analyzing the footprints of the animals on a blank sheet in conjunction with the formula established by Bain et al., (1989): SFI = 109.5 (ETS − NTS)/ NTS − 38.3 (EPL − NPL)/NPL + 13.3 (EIT − NIT)/ NIT − 8.8.PL (the distance between the third toe and the heel), TS (the distance between the first and fifth toes), and IT (the distance between the second and fourth toes). In this equation, "N" denotes the normal feet, while "E" refers to the experimental feet. According to this methodology, an SFI score of -100 indicates substantial injury, whereas a score close to 0 signifies normal functional activity.

Electrophysiological analzysis

All experimental groups underwent electrophysiological assessments on the 7th, 14th, 21st, and 28th day following the surgical procedure. A sedation protocol was used in order to expose the nerve for the evaluation, during which the amplitudes and conduction delays of the compound muscle action potential (CMAP) in the gastrocnemius muscle were measured. The study utilized E- Wave equipment (Science Beam, Iran) to record these parameters, with stimulation set at a frequency of 0.2 Hz and an intensity of 1000 mA, providing insights into the effectiveness of the surgical intervention on nerve recovery.

Gastrocnemius mass measurement

The gastrocnemius muscle mass ratio was utilized to conduct a rehabilitation assessment. This ratio was chosen as it provides a reliable measure of muscle recovery following nerve injury. Following the euthanasia of the animals, the gastrocnemius muscles were accurately excised and collected from the unaffected (non-operated) and affected (operated) regions, with their mass recorded while still in a moist state. To evaluate the percentage weight ratios, the muscle mass from the damaged regions was divided by the mass from the intact areas (Schiraldi et al., 2018).

Histological evaluations

After four weeks, the rats were euthanized for the extraction of the gastrocnemius muscle and sciatic nerve. The distal segments of the sciatic nerve and the middle third of the gastrocnemius muscle were fixed in a 10% formaldehyde solution (Merck, Germany). The samples were stored in fixation solution at 4°C until evaluation. Following treatment, the samples were embedded in paraffin (Bio-Optica, Italy) and sectioned at 5-µm intervals.

Hematoxylin and Eosin (H&E) staining

H&E staining was performed in order to examine the histological structure of the gastrocnemius muscle and measure muscle fiber diameters. After deparaffinization and rehydration, Hematoxylin was applied to these sections for 5 to 10 minutes, allowing the nuclei to take in dye and appear blue, followed by rinsing in running tap water. The cytoplasm and extracellular matrix were then stained pink with counterstaining of eosin for 30 seconds. Finally, the slides were washed in graded alcohols; cleared in substitute for xylene, and coverslipped for light microscopy.

Luxol Fast Blue (LFB) staining

After deparaffinization and rehydration, sections were incubated in Luxol Fast Blue solution (Sigma-Aldrich) overnight. The excess stain was then rinsed off with 95% ethyl alcohol and distilled water. The sections were differentiated in a 0.05% lithium carbonate solution for 30 seconds, followed by a 30-second rinse in 70% ethyl alcohol. A final rinse in distilled water was performed.

Immunohistochemistry

Immunohistochemical (IHC) techniques assessed myelin content and specific protein expression. The quantification of axonal neurofilaments and Schwann cells was conducted using primary antibodies, specifically rabbit anti-neurofilament-200 (NF-200, 1:100 dilution, Abcam) and rabbit anti-S100 (1:100 dilution, Abcam), with overnight incubation at 4 °C. After this, the sections were incubated for one hour at room temperature with a goat HRP-conjugated anti- rabbit secondary antibody diluted 1:1000 (Abcam). The visualization chromogen was Diaminobenzidine

(DAB) (SIGMAFAST™ DAB with Metal Enhancer, Sigma). The sections were subsequently examined using light microscopy. Five segments from each animal were selected at equivalent intervals for quantification purposes. Each segment was analyzed, and the total number of positive sections was averaged in five randomly chosen 400× microscopic fields (Novex, Netherlands).

We utilized ImageJ software (v 1.51, NIH, Bethesda, MD) to evaluate LFB color intensity and the number of axonal neurofilaments and Schwann cells. Muscle fiber diameters were assessed using photomicrographs of H&E-stained muscle tissue sections, which were analyzed with Digimizer software (v 4.3.0).

Total Oxidant Status (TOS)

We assessed total oxidant status (TOS) using a kit (Kiazist Company, Iran), which measured the concentrations of reactive nitrogen species (RNS) and reactive oxygen species (ROS) in all serum samples. In this experimental procedure, the presence of oxidants leads to the oxidation of ferrous iron (Fe^{2+}) to its ferric form (Fe^{3+}), which is subsequently stained by a chromogen. The resulting color intensity was quantified using a spectrophotometer set to a wavelength of 570 nm.

Statistical analysis

All statistical analyses were performed utilizing GraphPad Prism version 7.04. The current study's results are mean ± standard deviation (SD) for all data sets. The normality of the data was assessed using the Kolmogorov-Smirnov test. We compared the mean values across different groups using one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison tests to identify significant differences. A p-value of less than 0.05 was considered statistically significant.

RESULTS

GC/MS data analysis

All tests were performed in triplicate under the same conditions, and data were collected. Eight chemical substances were identified using GC/MS. The chemical compounds of the cinnamon extract, as determined by the GC/MS update library, are presented in Table 1. The main components were the cinnamaldehyde and MSM.

SFI

The SFI presented significant decreases in the treatment and clamp groups in the first week of post-operation compared to the sham rats. Motor operational rehabilitation improved in the treatment groups compared to the clamp group, as indicated by the SFI data after 28 days post- surgery. The data demonstrated that administering CAE at different dosing levels significantly and progressively affected the SFI. However, no significant difference was observed between the sets CAE 400 and CAE 100 in the treatment groups (Fig. 1).

Gastrocnemius muscle mass

In all rats, healthy and damaged foot muscles were compared regarding the gastrocnemius muscle mass ratio, and measurements were performed (Fig. 2). The sham group demonstrated the optimal data, with no muscle atrophy among

Table 1. The chemical contents of cinnamon aqueous extract.

Component	Area	Relation time(RT)	Quality
Cinnamaldehyde	63.29	11.018	97
Methyl sulfonyl methane (MSM)	21.8	3.877	90
Cinnamyl alcohol	4.83	11.767	96
cis-2-Methoxycinnamaldehyde	2.28	16.511	98
Coumarin	2.01	14.663	81
alpha-D-Glucopyranosiduronic acid	1.19	17.775	88
1-Methyl-2-pyrrolidone	1.27	6.068	95
Others	3.33		

The chemical contents of cinnamon aqueous extract. The contents were compared in terms of their mass spectra and relative retention time with those of standards. The extract compositions were designated based on corresponding retention time and spectra with the WILEY 275 (Wiley W9N11.L) library and the NIH Mass Spectral Database (NIST 11).

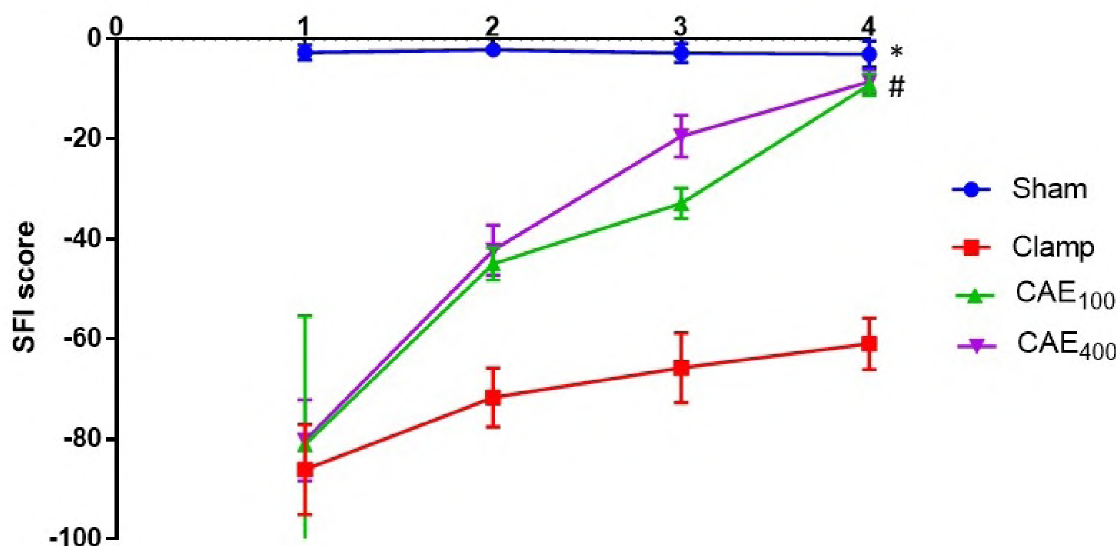

Fig. 1.- Motor Function recovery. The SFI decreased notably after the injury. The SFI value in the Sham group was better than that of other groups and had a significant difference compared to the CAE100 and CAE400 groups. The differences between the CAE groups were not significant. (*, # p<0.05, * the sham group compared to other groups, # CAE groups compare to Clamp group).

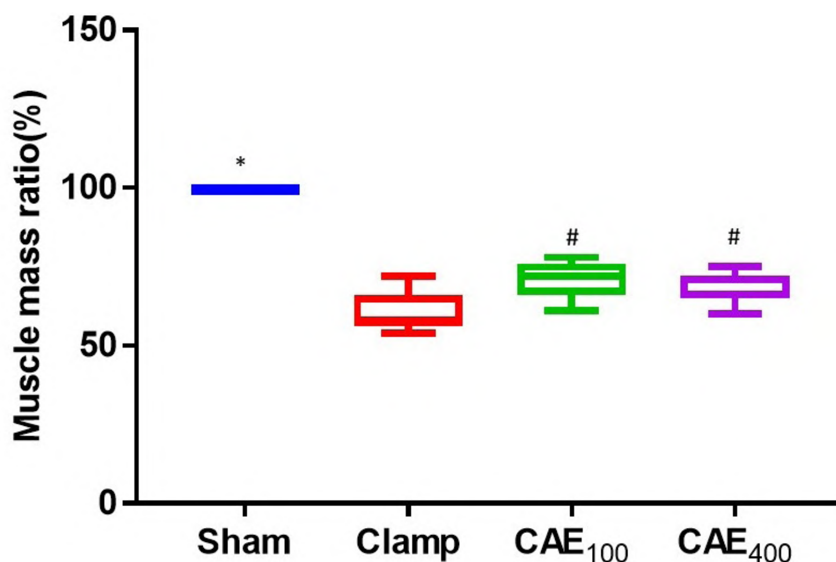

Fig. 2.- Gastrocnemius muscle weight. The gastrocnemius muscle on both sides (injured left and uninjured right) was weighed in all groups 4 weeks after surgery. There was no significant difference between the gastrocnemius muscle weight ratios of the CAE groups. There were statistically significant differences between the clamp and CAE groups (*p<0.05, compared to other groups; # p<0.05 compared to the clamp group).

other groups. The comparison of the treatment and clamp sets revealed a statistically significant difference ($p < 0.05$). However, no significant difference was observed in the treatment groups between CAE400 and CAE100.

Electrophysiological test

An electrophysiological experiment was applied to assess and evaluate motor functional rehabilitation after 28 days post-surgery. As presented in Fig. 3, the peak amplitude and the onset latency of CMAP were assessed for all groups. Statistically, considerable differences were identified between sham and clamp groups, and the latency was elevated in the clamp group compared to the other groups ($p < 0.05$). The clamp group demonstrated a reduction in amplitude, with statistically significant differences observed when compared to the sham group ($p < 0.05$). Furthermore, both latency and amplitude metrics in the CAE100 and

CAE400 groups exhibited marked improvement relative to the clamp group, reaching statistical significance ($p < 0.05$). The latency and amplitude measurements were similar between the CAE100 and CAE400 groups. However, the CAE400 group demonstrated better recovery than the CAE100 group ($P < 0.05$). Additionally, no statistically significant difference in latency was observed between the CAE100 and the clamp group ($p > 0.05$).

Total Oxidant Status (TOS)

The serum total oxidative status (TOS) level was measured for each test group, as illustrated in Fig. 4. The TOS levels in serum samples were assessed for all groups four weeks after the operation. The data showed that the TOS levels in the sham group (1.13 ± 0.06) and the clamp group (1.21 ± 0.08) were statistically comparable, and significantly elevated compared to the treatment groups. Serum TOS levels were substantially lower in the treatment groups than in other groups. No statistically significant difference was noted between the CAE400 and CAE100 groups. However, our results demonstrate that the groups treated with CAE showed a marked and statistically significant

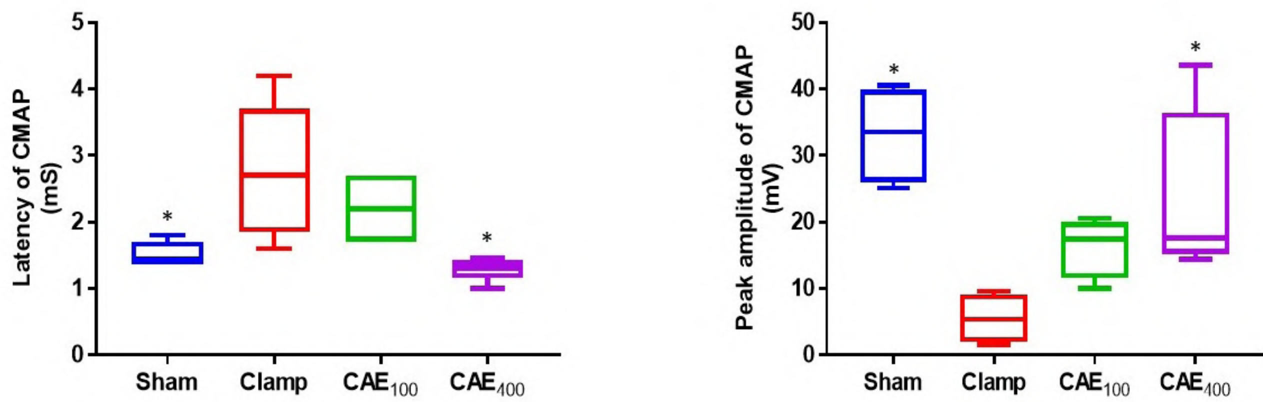

Fig. 3.- The electrophysiology test. The comparison of latency and amplitude of CMAP outcomes, 4 weeks after injury in all groups. The latency rose in the clamp group, compared to other groups, and there were no statistically significant differences between the clamp and CAE100 groups ($p>0.05$). On the other hand, there were statistically significant differences in the latency between the Cin400 and Sham groups with the clamp group ($p<0.05$). Moreover, the amplitude fell in the clamp group, and there were statistically significant differences between the sham and CAE400 groups and the clamp group ($p<0.05$). In the latency and amplitude of CMAP, significant differences were not found between the CAE groups (* $p<0.05$ compared to clamp group).

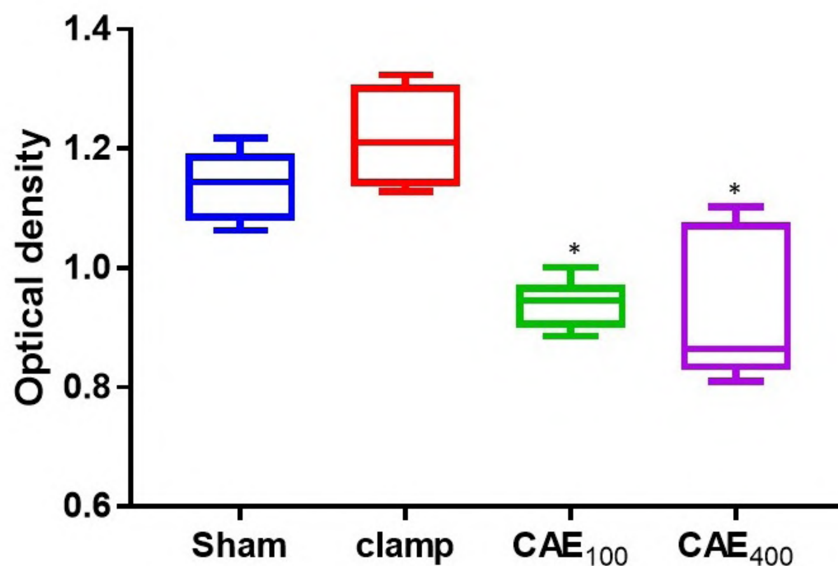

Fig. 4.- Assessment of Total Oxidant Status (TOS), 4 weeks after injury. The analysis showed that treatment with cinnamon extract decreased the amount of oxidant in serum samples. There were no statistically significant differences between the TOS levels in the sham and clamp groups. Besides, there was a significant difference between the sham and clamp groups and the treatment groups. (* $p<0.05$ compared to the sham and clamp groups).

reduction in total oxidative status (TOS) levels in the serum samples.

Histological evaluations

The diameter of gastrocnemius muscle fibers was compared among the clamp, treatment, and sham groups (Fig. 5). The sham set demonstrated the optimal data among the other sets, and no muscle atrophy was observed (Fig. 5A). In the clamp group, significant changes were observed, including a reduction in muscle fiber diameter and pronounced atrophy in the gastrocnemius muscle (Figure 5B). Additionally, there was a notable difference in muscle fiber diameter between the clamp and the sham and treatment groups (Figs. 5C-D). However, extract feeding led to an increase in the muscle fiber diameter of the gastrocnemius muscle. No statistically significant difference was detected between the two groups, CAE100 and CAE400.

The LFB staining was employed to evaluate nerve myelin. The color intensity across all groups was compared. The color intensity was higher in the sham group than in the other groups. Figure 6 demonstrates the positive impact of CAE on myelin formation following a sciatic nerve crush injury in rats. The graph illustrates that the sham group presented the highest color intensity, measuring 162.9 ± 9.48. In comparison, the clamp group showed a significant reduction in intensity, recording a value of 130.7 ± 5.26 (Figure 6B). However, using different CAE doses, these reductions were partially offset (Fig. 6C-D). The extract groups showed no significant difference in color intensity compared to the sham group ($p>0.05$). Conversely, a substantial difference was observed between the CAE100 and CAE400 groups compared to the clamp groups. However, no noticeable difference was found between the CAE100 and CAE400 groups.

The presence of neurofilaments and Schwann cells (SCs) was investigated using immunohistochemical staining. Data analysis demonstrated that the sham group had the highest number of SCs (Fig. 7). The comparison of the sham group and other groups showed a statistically significant difference ($p<0.05$). Although the extract feeding increased the number of SCs in the treatment sets, no considerable difference was identified between the treatment and clamp sets. No significant difference was found between CAE100 and CAE400 in the treatment sets. The anti-NF-200 immunohistochemistry data showed that the sham group had the optimal outcome among all groups. There was no statistically significant dif-

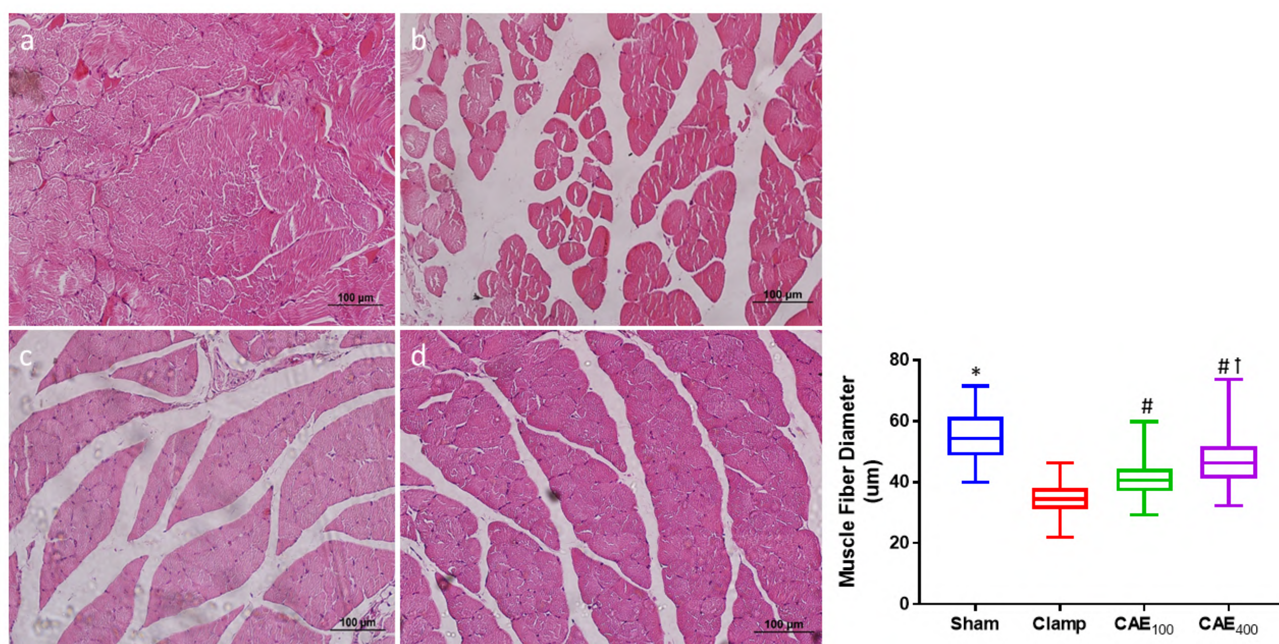

Fig. 5.- Hematoxylin and eosin (H&E) staining and muscle fiber diameter. The H&E staining in (a) the sham group, (b) the clamp group, (c) the CAE100 group, and (d) the CAE400 group, 4 weeks after injury. We measured the average diameter of rat gastrocnemius muscle fibers in all groups. The data showed that the extract improved the muscle diameter; however, there was a significant difference between the diameter of gastrocnemius muscle fibers in the sham and CAE groups. (*$p<0.05$ compared to all other groups, # $p<0.05$ compared to clamp group, # $p<0.05$ compared to CAE100). Scale bars = 100 µm.

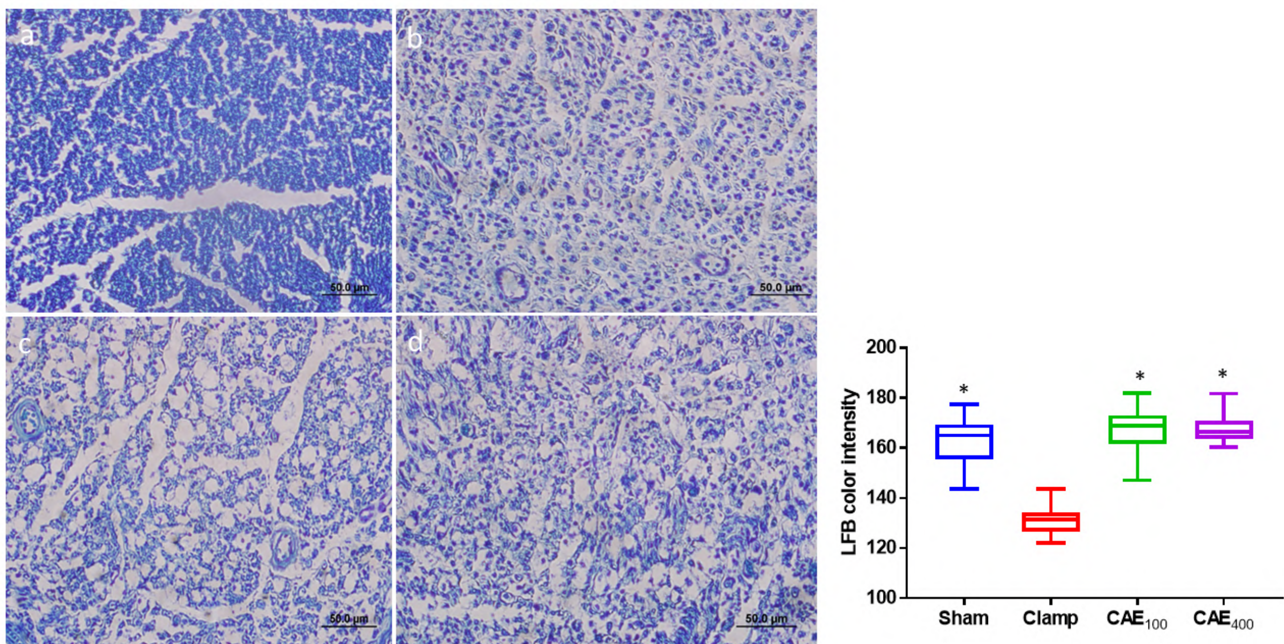

Fig. 6.- Luxol fast blue (LFB) staining. LFB staining in (a) the sham group, (b) the clamp group, (c) the CAE100 group, and (d) the CAE400 group, 4 weeks after the sciatic nerve crush injury. The quantification of staining intensity revealed that the injury reduced the myelin content; however, the treatment improved the myelination. There were no significant differences seen between the CAE groups and the sham group (* $p<0.05$ compared to the clamp group). Scale bars = 50 µm.

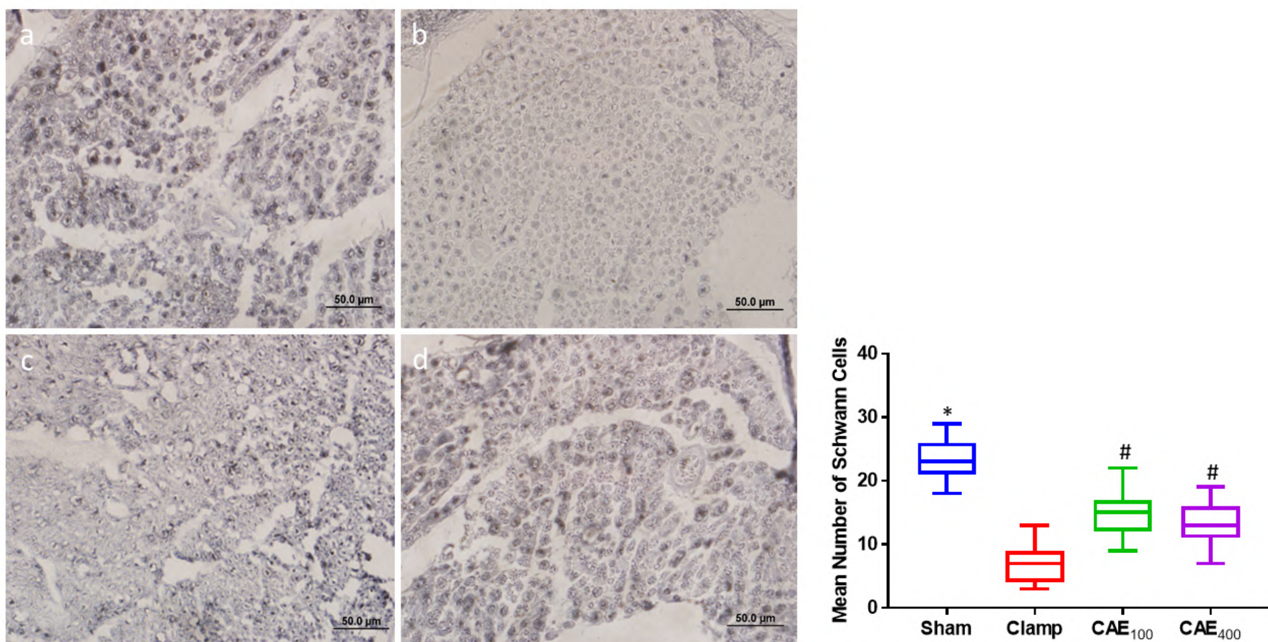

Fig. 7.- Immunohistochemical staining of Schwann cells, 4 weeks after injury in (a) the sham group, (b) the clamp group, (c) the CAE100 group, (d) the CAE400 group. The number of SCs in the sham group is higher than in the other groups, and the number is noticeably decreased in the clamp group. There was no significant difference between the CAE groups. However, there was a considerable difference between the sham group and the CAE groups. Scale bars = 50 µm. (* $p<0.05$ compared to the other groups, # $p<0.05$ compared to the clamp group).

ference between the treatment groups of CAE100 and CAE400. However, a considerable distinction was noted when comparing these treatment groups to the clamp group. No meaningful differences were detected when comparing them with the sham group (Fig. 8).

DISCUSSION

Peripheral nerve injury represents a significant and prevalent concern in contemporary society, and despite advancements in treatment methodologies, outcomes often remain unsatisfactory. This underscores the need for further research

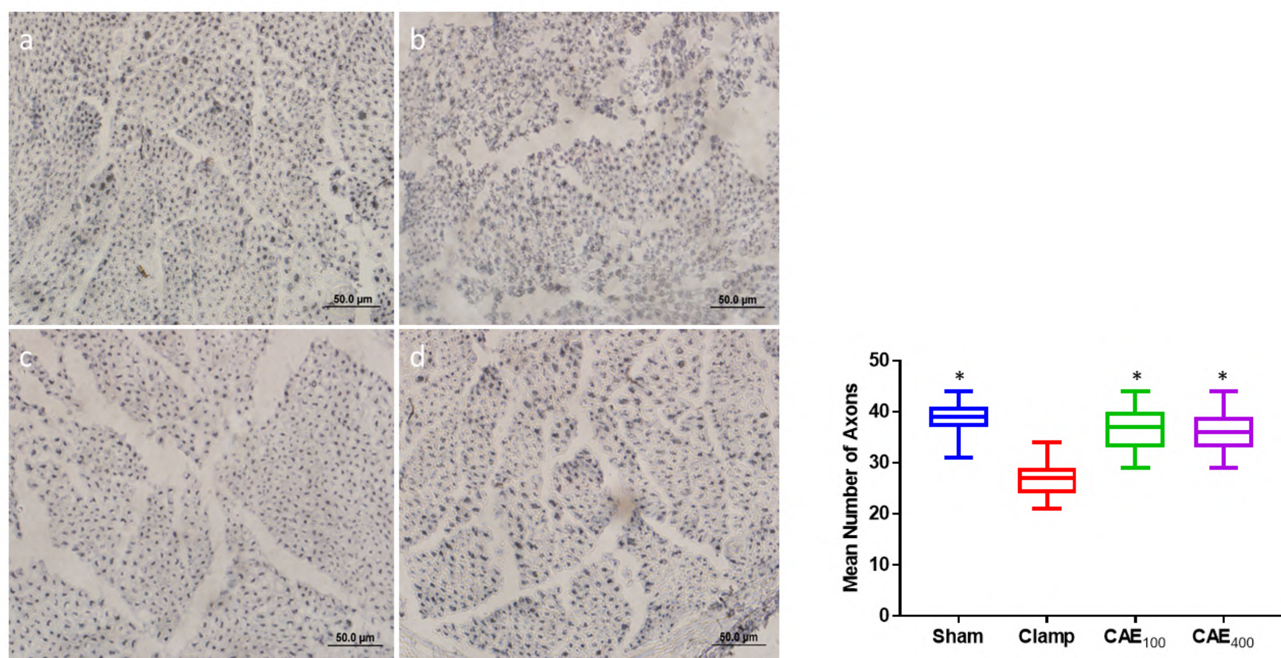

Fig. 8.- Nerve regeneration assessment. Immunohistochemistry staining for regenerated nerves 4 weeks after surgery in (a) the sham group, (b) the injury group, (c) the CAE100 group, and (d) the CAE400 group. The quantification of the axons showed that the injury reduced the number of axons; however, the CAE feeding improved nerve regeneration. There was no significant difference between the number of axons in the sham and CAE groups. At the same time, there was a significant difference between the number of axons in the clamp group and the other groups. Scale bars = 50 µm. (* $p<0.05$, compared to the clamp group).

that may identify effective therapeutic strategies or pharmacological agents to enhance recovery. A severe injury to a peripheral nerve, such as sciatica, typically initiates a brief episode of local ischemia in the affected region. This ischemic event disrupts the electrolyte balance within the nerve and reduces endoneurial capillary blood flow. Consequently, these alterations trigger the release of various chemical mediators, increase vascular permeability, and compromise the integrity of the blood-nerve barrier. Such processes lead to endothelial and intraneural edema, accompanied by an inflammatory response that induces metabolic disturbances within the tissue. Following these pathological changes, toxic oxygen metabolites — including hydrogen peroxide (H2O2), superoxide anions, and hydroxyl radicals — accumulate in the damaged area alongside polymorphonuclear leukocytes. Released free radicals and cytokines from neutrophils further exacerbate nerve damage (Kurtoglu et al., 2004; Morani and Bodhankar, 2008). Subsequently, histological alterations occur, culminating in Wallerian degeneration in the distal segment of the injury (Dinh et al., 2009).

Consequently, therapeutic strategies to protect neurons and nerve tissue must address oxidative stress, emphasizing the importance of antioxidant-active neuroprotective agents (Pekdemir et al., 2024). Evidence suggests that antioxidant enzymes, including catalase, superoxide dismutase, and glutathione-S-transferase, play a crucial role in regenerating peripheral nerves following injury (Lanza et al., 2012). Furthermore, antioxidant compounds such as melatonin and N-acetyl cysteine have demonstrated promising effects in accelerating the repair of the sciatic nerve after it has been subjected to crushing and amputation (Zencirci et al., 2010; Welin et al., 2009). The aqueous and alcoholic extracts of cinnamon and its derivatives exhibit antioxidant properties, effectively mitigating oxidative stress induced by reactive oxygen and nitrogen species (Jahromi et al., 2020; Gulcin et al., 2019; Muhammad and Dewettinck, 2017; Jang et al., 2007; Okawa et al., 2001).

In the current study, a Crush model of sciatic nerve injury was developed in male rats to assess the therapeutic effects of cinnamon aqueous extract at dosages of 100 and 400 mg/kg/day, focusing on the histological and motor recovery outcomes in the subjects. The present investigation revealed a reduction in the quantities of myelin,

nerve fibers, and Schwann cells following a crush injury to the sciatic nerve. Conversely, there was an observed increase in total serum oxidant levels, corroborating findings from previous studies. Additionally, assessments of the motor function index (SFI), along with measurements of muscle cell diameter and the wet weight of the gastrocnemius muscle, demonstrated a beneficial effect of cinnamon aqueous extract in the treatment groups, facilitating the nerve repair process. Histological analyses indicated a significant enhancement in myelin content and nerve fiber density in the treatment groups receiving 100 and 400 mg/kg/day doses. Furthermore, while the number of Schwann cells increased in both treatment groups relative to the crush group, this change did not reach statistical significance.

Several studies have indicated that cinnamon contains constituents with antioxidant and anti-inflammatory properties (Pagliari et al., 2023; Gunawardena et al., 2015; Mateos-Martín et al., 2012). The results of our analysis corroborate this finding. The primary components of cinnamon extract (CE) identified in the current study are Cinnamaldehyde and Methyl sulfonyl methane (MSM).

Cinnamaldehyde (Cin), the principal constituent of cinnamon extract, is classified within the group of phenolic compounds, specifically as an aldehyde. This compound imparts the distinctive flavor and aroma associated with cinnamon. It is associated with a range of beneficial properties, including antioxidant, antimicrobial, anti-diabetic, anti-cancer, anti-inflammatory, and neuroprotective effects (Roghani et al., 2017; Stavinoha and Vattem 2015; Calsamiglia et al., 2007). Evidence suggests that Cin functions as a natural anti-inflammatory and antioxidant mediator, with studies demonstrating its regenerative effects and enhancement of functional recovery following nerve damage (Jahromi et al., 2020; Roghani et al., 2017; Chen et al., 2016; Pyo et al., 2013). The therapeutic mechanisms underpinning the effects of Cin following sciatic nerve injury possibly involve the regulation of inflammatory mediators and oxidative stress pathways. (Jahromi et al., 2020; Roghani et al., 2017; Chao et al., 2008). It effectively reduces the production of pro-inflammatory cytokines, thereby diminishing the inflammatory response. This reduction occurs through the inhibition of immune cell activation, particularly in macrophages and T-cells, which are crucial for cytokine production. Cinnamaldehyde downregulates genes encoding cytokines such as TNF-α, IL-1β, and IL-6 by interfering with transcription factors like NF-κB and AP-1, essential for the transcription of these inflammatory mediators (Liao et al., 2008; Wondrak et al., 2010; Fu et al., 2017). Additionally, Cin inhibits the phosphorylation and degradation of IκB, preventing the release of NF-κB dimers from the cytoplasm, thereby blocking their nuclear translocation and subsequent activation of pro-inflammatory genes.

Moreover, researchers have demonstrated that cinnamon possesses anti-inflammatory properties by inhibiting the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). Cinnamaldehyde modulates the expression of antioxidant response genes via the Nrf2 pathway, leading to an increase in antioxidant enzymes like superoxide dismutase (SOD) and glutathione peroxidase (Wondrak et al., 2010; Wang et al., 2015; Uchi et al., 2017). This upregulation helps neutralize reactive oxygen species (ROS), reducing oxidative damage to cellular components, which is vital in preventing neuronal apoptosis following nerve injury (Lv et al., 2017; Rashidi et al., 2021).

Following an injury, Schwann cells and macrophages express COX-2, which plays a significant role in the inflammatory response associated with nerve injury (Xie et al., 2022; Shin et al., 2003). COX-2 is recognized as an inflammatory mediator that modulates inflammatory processes in various neurological disorders (Belkas et al., 2004). This mediator promotes the expression of additional pro-inflammatory cytokines, exacerbating inflammation and contributing to nerve degeneration post-injury (Bedoui et al., 2023). A study by Klegeris and McGeer (2002) indicated that the inhibition of COX-2 could mitigate the toxic effects exerted by macrophages and glial cells in vitro. In light of the observed improvements in sciatic nerve repair in our study, it is plausible that the aqueous extract of cinnamon may similarly facilitate the recovery process. Conversely, generating

reactive oxygen species (ROS) in neuronal injuries is recognized as a primary contributor to nerve damage. It is posited that free radicals can impede axonal growth (Wu et al., 2020), and reducing the concentration of free radicals in the injury site may enhance the reduction of inflammation and edema (Sun et al., 2018).

Cin also stimulates the synthesis of neurotrophic factors, notably nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), which are essential for neuronal survival and axonal growth (Lykissas et al., 2007). By activating the TrkA receptor associated with NGF, Cin enhances downstream signaling pathways such as PI3K/Akt and MAPK/ERK, which are critical for neuronal growth and differentiation (Moosavi et al., 2015; Yuan et al., 2018).

The second component, methylsulfonyl methane (MSM), is a naturally occurring organosulfur compound found in trace amounts in certain green plants, fruits, and vegetables. Also called dimethyl sulfone, MSM is a safe nutritional supplement for human consumption (Parcell, 2002).

MSM also acts as a potent antioxidant, effectively reducing oxidative stress and protecting neuronal integrity. By increasing levels of glutathione, a critical intracellular antioxidant, MSM aids in maintaining redox homeostasis within nerve cells (Kim et al., 2015; Butawan et al., 2020). Also, one investigation revealed that MSM significantly decreased the production of malondialdehyde (MDA), myeloperoxidase (MPO), and IL-1β, while simultaneously increasing levels of glutathione (GSH) and catalase (CAT) (Amirshahrokhi et al., 2011).

Furthermore, MSM balances the inflammatory response by downregulating the production of pro-inflammatory cytokines while promoting the synthesis of anti-inflammatory mediators. Research has indicated that MSM possesses anti-inflammatory properties; it reduces the expression of pro-inflammatory cytokines such as TNF-α IL-1, and IL-6 and the activity of inflammasomes in immune cells by modulating signaling pathways, including NF-κB (Vickers 2017; Kloesch et al., 2011; Kim et al., 2009; Mohammadi et al., 2012). These properties are crucial for preventing chronic inflammatory states that can hinder nerve repair.

Following treatment with aqueous cinnamon extract at 100 and 400 mg/kg/day dosages, our findings indicated a significant reduction in oxidant levels in both treatment groups when compared to the control group subjected to crushing. These results corroborate the antioxidant capabilities of cinnamon, which is consistent with previous research. Furthermore, it has been documented that those factors promoting the growth and proliferation of Schwann cells enhance the antioxidant capacity of the surrounding environment, as these cells play a role in diminishing oxidant levels and consequently reducing neuronal damage (Balakrishnan et al., 2021). The results of this study revealed an increase in the number of Schwann cells in the treatment group compared to the control group. Although this increase was not statistically significant, the observed improvements in other symptoms suggest that these cells may reduce oxidants.

Schwann cells are known to secrete neurotrophic factors, including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin-3, which are essential for the survival and repair of neurons (Godinho et al., 2020; Azizi et al., 2014). Research conducted by Jana et al. (2013) indicates that cinnamon and its metabolite, sodium benzoate, enhance the expression of neurotrophic factors such as BDNF and neurotrophin-1.

Our immunohistochemical staining data, along with the observed increase in Schwann cell numbers following treatment with aqueous cinnamon extract, support the notion that these cells secrete neurotrophic factors. This secretion is associated with improvements in motor parameters, body weight, and the diameter of gastrocnemius muscle cells, thereby affirming the role of Schwann cells in stimulating nerve fiber growth post-injury, as corroborated by other studies (Jahromi et al., 2020; Kang et al., 2003).

Additionally, Cin activates the PI3K/Akt and MAPK/ERK pathways and increases VEGF secretion, promoting angiogenesis and wound healing (Yuan et al., 2018). By enhancing blood flow to the

injured nerve area, cinnamaldehyde facilitates the delivery of essential nutrients and oxygen, crucial for cellular repair and regeneration.

Overall, the sciatica functional index (SFI) is regarded as the most significant assessment method for evaluating the success and efficacy of interventions aimed at nerve repair (Li et al., 2023; Farahpour and Ghayour, 2014; Mohammadi et al., 2013). The results of the current study indicate that treatment with aqueous cinnamon extract at doses of 100 and 400 mg led to improvements in SFI compared to the crush group after two weeks, with a notable increase in the fourth week for the 400 mg treatment group. Given that walking necessitates coordination among sensory input, motor responses, and cortical function (Charalambous and Hadjipapas,2022), gait analysis via the SFI is considered a thorough and effective evaluation tool (Li et al., 2023; Farahpour and Ghayour, 2014). It is posited that the SFI test offers more excellent reliability and comprehensiveness than other histomorphometric methods for investigating peripheral nerve repair (Arcot et al., 2012; Joung et al., 2010).

In conclusion, the oral administration of cinnamon aqueous extract at dosages of 100 and 400 mg/kg/day over 28 days in a rat model of sciatic nerve injury demonstrated significant improvements in sciatic functional index (SFI), wet weight of the gastrocnemius muscle, muscle cell diameter, myelin content, and the number of Schwann cells. These findings suggest that the bioactive components of cinnamon aqueous extract may facilitate nerve repair following injury by mitigating inflammation and promoting the clearance of detrimental oxidants. Consequently, cinnamon aqueous extract holds potential for future applications in the repair of damaged peripheral nerves.

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REFERENCES

AMAN M, ZIMMERMANN KS, THIELEN M, THOMAS B, DAESCHLER S, BOECKER AH, STOLLE A, BIGDELI AK, KNESER U, HARHAUS L (2022) An epidemiological and etiological analysis of 5026 peripheral nerve lesions from a European level I trauma center. *JPM*, 12(10): 1673.

AMIRSHAHROKHI K, BOHLOOLI S, CHINIFROUSH M (2011) The effect of methylsulfonylmethane on the experimental colitis in the rat. *Toxicol Appl Pharmacol*, (253): 197-202.

ARCOT R, RAMAKRISHNAN K, RAO S (2012) Peripheral and cranial nerve sheath tumors—a clinical spectrum. *Indian J Surg*, 74: 371-375.

ATIK B, ERKUTLU I, TERCAN M, BUYUKHATIPOGLU H, BEKERECIOGLU M, PENCE S (2011) The effects of exogenous melatonin on peripheral nerve regeneration and collagen formation in rats. *J Surg Res*, (166): 330-336.

AZIZI A, AZIZI S, HESHMATIAN B, AMINI K (2014) Improvement of functional recovery of transected peripheral nerve by means of chitosan grafts filled with vitamin E, pyrroloquinoline quinone and their combination. *Int J Surg*, 12: 76-82.

BAIN JR, MACKINNON SE, HUNTER DA (1989) Functional evaluation of complete sciatic, peroneal, and posterior tibial nerve lesions in the rat. *Plast Reconstr Surg*, 83: 129-138.

BALAKRISHNAN A, BELFIORE L, CHU TH, FLEMING T, MIDHA R, BIERNASKIE J, SCHUURMANS C (2021) Insights into the role and potential of Schwann cells for peripheral nerve repair from studies of development and injury. *Front Mol Neurosci*, 13: 608442.

BEDOUI Y, DE LARICHAUDY D, DANIEL M, AH-PINE F, SELAMBAROM J, GUIRAUD P, GASQUE P (2023) Deciphering the role of Schwann cells in inflammatory peripheral neuropathies post alphavirus infection. *Cells*, 12: 100.

BELKAS JS, SHOICHET MS, MIDHA R (2004) Peripheral nerve regeneration through guidance tubes. *Neurol Res*, 26: 151-160.

BUTAWAN M, BENJAMIN RL, BLOOMER RJ (2020) Chapter 27 - Methylsulfonylmethane as an antioxidant and its use in pathology. In: Preedy VR (ed.) *Pathology*. Academic Press.

CALSAMIGLIA S, BUSQUET M, CARDOZO P, CASTILLEJOS L, FERRET A (2007) Invited review: essential oils as modifiers of rumen microbial fermentation. *J Dairy Sci*, 90: 2580-2595.

CHAO LK, HUA K-F, HSU H-Y, CHENG S-S, LIN I-F, CHEN C-J, CHEN S-T, CHANG S-T (2008) Cinnamaldehyde inhibits pro-inflammatory cytokines secretion from monocytes/macrophages through suppression of intracellular signaling. *Food Chem Toxicol*, 46: 220-231.

CHARALAMBOUS CC, HADJIPAPAS A (2022) Is there frequency-specificity in the motor control of walking? The putative differential role of alpha and beta oscillations. *Front Syst Neurosci*, 16: 922841.

CHEN Y-F, WANG Y-W, HUANG W-S, LEE M-M, WOOD WG, LEUNG Y-M, TSAI H-Y (2016) Trans-cinnamaldehyde, an essential oil in cinnamon powder, ameliorates cerebral ischemia-induced brain injury via inhibition of neuroinflammation through attenuation of iNOS, COX-2 expression and NFκ-B signaling pathway. *Neuromolecular Med*, 18: 322-333.

DAVOUDI F, RAMAZANI E (2024) Antioxidant and anti-inflammatory effects of Cinnamomum species and their bioactive compounds: An updated review of the molecular mechanisms. *Physiol Pharmacol*, 28: 99-116.

DESAI N, ARORA N, GUPTA A (2022) Chemotherapy-induced peripheral neuropathy. *JAMA Internal Medicine*, 182: 766-767.

DINH P, HAZEL A, PALISPIS W, SURYADEVARA S, GUPTA R (2009) Functional assessment after sciatic nerve injury in a rat model. *Microsurgery*, 29: 644-649.

FARAHPOUR MR, GHAYOUR SJ (2014) Effect of in situ delivery of acetyl-L-carnitine on peripheral nerve regeneration and functional recovery in transected sciatic nerve in rat. *Int J Surg*, 12: 1409-1415.

FARONI A, MOBASSERI SA, KINGHAM PJ, REID AJ (2015) Peripheral nerve regeneration: experimental strategies and future perspectives. *Adv Drug Deliv Rev*, 82: 160-167.

FENG X, YUAN W (2015) Dexamethasone enhanced functional recovery after sciatic nerve crush injury in rats. *Biomed Res Int*, 2015: 627923.

FU Y, YANG P, ZHAO Y, ZHANG L, ZHANG Z, DONG X, WU Z, XU Y, CHEN Y (2017) trans-Cinnamaldehyde inhibits microglial activation and improves neuronal survival against neuroinflammation in BV2 microglial cells with lipopolysaccharide stimulation. *Evid Based Complement Alternat Med*, 2017: 4730878.

GIBBONS CH (2020) Diabetes and metabolic disorders and the peripheral nervous system. *Continuum (Minneapolis, Minn.)*, 26(5): 1161-1183.

GODINHO MJ, STAAL JL, KRISHNAN VS, HODGETTS SI, POLLETT MA, GOODMAN DP, TEH L, VERHAAGEN J, PLANT GW & HARVEY AR (2020) Regeneration of adult rat sensory and motor neuron axons through chimeric peroneal nerve grafts containing donor Schwann cells engineered to express different neurotrophic factors. *Exp Neurol*, (330): 113355.

GULCIN I, KAYA R, GOREN AC, AKINCIOGLU H, TOPAL M, BINGOL Z, CETIN ÇAKMAK K, OZTURK SARIKAYA SB, DURMAZ L, ALWASEL S (2019) Anticholinergic, antidiabetic and antioxidant activities of cinnamon (cinnamomum verum) bark extracts: polyphenol contents analysis by LC-MS/MS. *Int J Food Prop*, 22: 1511-1526.

GUNAWARDENA D, KARUNAWEERA N, LEE S, VAN DER KOOY F, HARMAN DG, RAJU R, BENNETT L, GYENGESI E, SUCHER NJ, MÜNCH G (2015) Anti-inflammatory activity of cinnamon (C. zeylanicum and C. cassia) extracts - identification of E- cinnamaldehyde and o-methoxy cinnamaldehyde as the most potent bioactive compounds. *Food Funct*, 6(3): 910-919.

HICKS CW, SELVIN E (2019) Epidemiology of peripheral neuropathy and lower extremity disease in diabetes. *Current Diabetes Rep*, 19: 1-8.

HO S-C, CHANG K-S, CHANG P-W (2013) Inhibition of neuroinflammation by cinnamon and its main components. *Food Chem*, 138: 2275-2282.

HOUSCHYAR K, MOMENI A, PYLES M, CHA J, MAAN Z, DUSCHER D, JEW O, SIEMERS F, SCHOONHOVEN JV (2016) The role of current techniques and concepts in peripheral nerve repair. *Plast Surg Int*, 2016: 4175293.

IZHIMAN Y, ESFANDIARI L (2024) Emerging role of extracellular vesicles and exogenous stimuli in molecular mechanisms of peripheral nerve regeneration. *Front Cell Neurosci*, 18: 1368630.

JAHROMI Z, MOHAMMADGHASEMI F, MOHARRAMI KASMAIE F, ZAMINY A (2020) Cinnamaldehyde enhanced functional recovery after sciatic nerve crush injury in rats. *Cells Tissues Organs*, 209: 43-53.

JANA A, MODI KK, ROY A, ANDERSON JA, VAN BREEMEN RB, PAHAN K (2013) Up-regulation of neurotrophic factors by cinnamon and its metabolite sodium benzoate: therapeutic implications for neurodegenerative disorders. J *Neuroimmune Pharmacol*, 8: 739-755.

JANG H-D, CHANG K-S, HUANG Y-S, HSU C-L, LEE S-H, SU M-S (2007) Principal phenolic phytochemicals and antioxidant activities of three Chinese medicinal plants. *Food Chem*, 103: 749-756.

JOUNG I, YOO M, WOO JH, CHANG CY, HEO H, KWON YK (2010) Secretion of EGF-like domain of heregulinβ promotes axonal growth and functional recovery of injured sciatic nerve. *Mol Cells*, 30: 477-484.

KANG H, TIAN L, THOMPSON W (2003) Terminal Schwann cells guide the reinnervation of muscle after nerve injury. *J Neurocytol*, 32: 975-985.

KIM S-H, SMITH AJ, TAN J, SHYTLE RD, GIUNTA B (2015) MSM ameliorates HIV-1 Tat induced neuronal oxidative stress via rebalance of the glutathione cycle. *Am J Translat Res*, 7(2): 328-338.

KIM YH, KIM DH, LIM H, BAEK D-Y, SHIN H-K, KIM J-K (2009) The anti-inflammatory effects of methylsulfonylmethane on lipopolysaccharide-induced inflammatory responses in murine macrophages. *Biol Pharm Bull*, 32: 651-656.

KLEGERIS A, MCGEER PL (2002) Cyclooxygenase and 5-lipoxygenase inhibitors protect against mononuclear phagocyte neurotoxicity. *Neurobiol Aging*, 23: 787-794.

KLOESCH B, LISZT M, BROELL J, STEINER G (2011) Dimethyl sulphoxide and dimethyl sulphone are potent inhibitors of IL-6 and IL-8 expression in the human chondrocyte cell line C-28/I2. *Life Sci*, 89: 473-478.

KOCAOGLU S, AKTAS O, ZENGI O, TUFAN A, GUZEY FK (2017) Effects of alpha lipoic acid on motor function and antioxidant enzyme activity of nerve tissue after sciatic nerve crush injury in rats. *Turk Neurosurg*, 28(5):740-747.

KOUYOUMDJIAN JA, GRAÇA CR, FERREIRA VFM (2017) Peripheral nerve injuries: A retrospective survey of 1124 cases. *Neurology India*, 65(3): 551-555.

KURTOGLU Z, OZTURK A, BAGDATOGLU C, TURAC A, CAMDEVIREN H, UZMANSEL D, AKTEKIN M (2004) Effect of trapidil on the sciatic nerve with crush injury: a light microscopic study. *Neuroanatomy*, 3: 54-58.

LANZA C, RAIMONDO S, VERGANI L, CATENA N, SÉNÈS F, TOS P, GEUNA S (2012) Expression of antioxidant molecules after peripheral nerve injury and regeneration. *J Neurosci Res*, 90: 842-848.

LI D, YANG Q, LIU X, JIA J, LIU G, BAI K, JIA S, PENG J, YU F (2023) Experimental study on the repair of peripheral nerve injuries via simultaneously coapting the proximal and distal ends of peripheral nerves to the side of nearby intact nerves. *Front Neurol*, 14: 1088983.

LI R, LI DH, ZHANG HY, WANG J, LI XK, XIAO J (2020) Growth factors-based therapeutic strategies and their underlying signaling mechanisms for peripheral nerve regeneration. *Acta Pharmacol Sin*, 10: 1289-1300.

LIAO B-C, HSIEH C-W, LIU Y-C, TZENG T-T, SUN Y-W, WUNG B-S (2008) Cinnamaldehyde inhibits the tumor necrosis factor-α-induced expression of cell adhesion molecules in endothelial cells by suppressing NF-κB activation: Effects upon IκB and Nrf2. *Toxicol Appl Pharmacol*, 229: 161-171.

LIU H, LV P, ZHU Y, WU H, ZHANG K, XU F, ZHENG L, ZHAO J (2017) Salidroside promotes peripheral nerve regeneration based on tissue engineering strategy using Schwann cells and PLGA: in vitro and in vivo. *Sci Rep*, 7: 39869.

LV C, YUAN X, ZENG H-W, LIU R-H, ZHANG W-D (2017) Protective effect of cinnamaldehyde against glutamate-induced oxidative stress and apoptosis in PC12 cells. *Eur J Pharmacol*, 815: 487-494.

LYKISSAS MG, BATISTATOU AK, CHARALABOPOULOS KA, BERIS AE (2007) The role of neurotrophins in axonal growth, guidance, and regeneration. *Curr Neurovasc Res*, 4: 143-151.

MA W, EISENACH J (2003) Cyclooxygenase 2 in infiltrating inflammatory cells in injured nerve is universally up-regulated following various types of peripheral nerve injury. *Neuroscience*, 121: 691-704.

MATEOS-MARTÍN ML, FUGUET E, QUERO C, PÉREZ-JIMÉNEZ J, TORRES JL (2012) New identification of proanthocyanidins in cinnamon (Cinnamomum zeylanicum L.) using MALDI-TOF/TOF mass spectrometry. *Anal Bioanal Chem*, 402: 1327-1336.

MOHAMMADI R, HIRSAEE M-A, AMINI K (2013) Improvement of functional recovery of transected peripheral nerve by means of artery grafts filled with diclofenac. *Int J Surg*, 11: 259-264.

MOHAMMADI S, NAJAFI M, HAMZEIY H, MALEKI-DIZAJI N, PEZESHKIAN M, SADEGHI-BAZARGANI H, DARABI M, MOSTAFALOU S, BOHLOOLI S, GARJANI A (2012) Protective effects of methylsulfonylmethane on hemodynamics and oxidative stress in monocrotaline-induced pulmonary hypertensive rats. *Adv Pharmacol Sci*, 2012: 507278.

MOHARRAMI KASMAIE F, JAHROMI Z, GAZOR R, ZAMINY A (2019) Comparison of melatonin and curcumin effect at the light and dark periods on regeneration of sciatic nerve crush injury in rats. *EXCLI J*, 18: 653-665.

MOOSAVI F, HOSSEINI R, SASO L, FIRUZI O (2015) Modulation of neurotrophic signaling pathways by polyphenols. *Drug Des Devel Ther*, 10: 23-42.

MORANI AS, BODHANKAR SL (2008) Neuroprotective effect of vitamin E acetate in models of mononeuropathy in rats. *Neuroanatomy*, 7: 33-37.

MUHAMMAD DRA, DEWETTINCK K (2017) Cinnamon and its derivatives as potential ingredient in functional food—A review. *Int J Food Prop*, 20: 2237-2263.

MURPHY RNA, DE SCHOULEPNIKOFF C, CHEN JHC, COLUMB MO, BEDFORD J, WONG JK, REID AJ (2023) The incidence and management of peripheral nerve injury in England (2005-2020). *JPRAS*, 80: 75-85.

OKAWA M, KINJO J, NOHARA T, ONO M (2001) DPPH (1, 1-diphenyl-2-picrylhydrazyl) radical scavenging activity of flavonoids obtained from some medicinal plants. *Biol Pharm Bull*, 24: 1202-1205.

PAGLIARI S, FORCELLA M, LONATI E, SACCO G, ROMANIELLO F, ROVELLINI P, FUSI P, PALESTINI P, CAMPONE L, LABRA M, BULBARELLI

A, BRUNI I (2023) Antioxidant and anti-inflammatory effect of cinnamon (Cinnamomum verum J. Presl) bark extract after in vitro digestion simulation. *Foods*, 12(3): 452.

PARCELL S (2002) Sulfur in human nutrition and applications in medicine. *Altern Med Rev*, 7: 22-44.

PATRA K, BOSE S, SARKAR S, RAKSHIT J, JANA S, MUKHERJEE A, ROY A, MANDAL DP, BHATTACHARJEE S (2012) Amelioration of cyclophosphamide induced myelosuppression and oxidative stress by cinnamic acid. *Chem Biol Interact*, 195: 231-239.

PEKDEMIR B, RAPOSO A, SARAIVA A, LIMA MJ, ALSHARARI ZD, BINMOWYNA MN, KARAV S (2024) Mechanisms and potential benefits of neuroprotective agents in neurological health. *Nutrients*, 16: 4368.

PYO J-H, JEONG Y-K, YEO S, LEE J-H, JEONG M-Y, KIM S-H, CHOI Y-G, LIM S (2013) Neuroprotective effect of trans-cinnamaldehyde on the 6-hydroxydopamine-induced dopaminergic injury. *Biol Pharm Bull*, 36: 1928-1935.

RANASINGHE P, PERERA S, GUNATILAKE M, ABEYWARDENE E, GUNAPALA N, PREMAKUMARA S, PERERA K, LOKUHETTY D, KATULANDA P (2012) Effects of Cinnamomum zeylanicum (Ceylon cinnamon) on blood glucose and lipids in a diabetic and healthy rat model. *Pharmacognosy Res*, 4(2): 73-79.

RASHIDI R, MOALLEM SA, MOSHIRI M, HADIZADEH F, ETEMAD L (2021) Protective effect of cinnamaldehyde on METH-induced neurotoxicity in PC12 cells via inhibition of apoptotic response and oxidative stress. *IJPR*, 20(2): 135-143.

ROCK KL, KONO H (2008) The inflammatory response to cell death. *Annu Rev Pathol*, 3: 99-126.

ROGHANI M, MEHRAEIN F, ZAMANI M, NEGAHDAR F, SHOJAEE A (2017) The effects of aqueous cinnamon bark extract and cinnamaldehyde on neurons of substantia nigra and behavioral impairment in a mouse model of Parkinson's disease. *JBCP*, 5: 27-32.

SCHIRALDI L, SOTTAZ L, MADDURI S, CAMPISI C, ORANGES CM, RAFFOUL W, KALBERMATTEN DF, DI SUMMA PG (2018) Split-sciatic nerve surgery: A new microsurgical model in experimental nerve repair. *J Plast Reconstr Aesthet Surg*, 71: 557-565.

SERETNY M, CURRIE GL, SENA ES, RAMNARINE S, GRANT R, MACLEOD MR, COLVIN LA, FALLON M (2014) Incidence, prevalence, and predictors of chemotherapy-induced peripheral neuropathy: a systematic review and meta-analysis. *Pain*, 155: 2461-2470.

SHIN T, LEE Y, SIM KB (2003) Involvement of cyclooxygenase-1 and-2 in the sciatic nerve of rats with experimental autoimmune neuritis. *Immunol Invest*, 32: 123-130.

STAVINOHA R, VATTEM D (2015) Potential neuroprotective effects of cinnamon. *ICMJE*, 8: 24-46.

SUN M-S, JIN H, SUN X, HUANG S, ZHANG F-L, GUO Z-N, YANG Y (2018) Free radical damage in ischemia-reperfusion injury: an obstacle in acute ischemic stroke after revascularization therapy. *Oxid Med Cell Longev*, 2018: 3804979.

UCHI H, YASUMATSU M, MORINO-KOGA S, MITOMA C, FURUE M (2017) Inhibition of aryl hydrocarbon receptor signaling and induction of NRF2-mediated antioxidant activity by cinnamaldehyde in human keratinocytes. *J Dermatol Sci*, 85: 36-43.

VICKERS NJ (2017) Animal communication: when I'm calling you, will you answer too? Curr Biol, 27: R713-R715.

WANG F, PU C, ZHOU P, WANG P, LIANG D, WANG Q, HU Y, LI B, HAO X (2015) Cinnamaldehyde prevents endothelial dysfunction induced by high glucose by activating Nrf2. Cell Physiol Biochem, 36: 315-324.

WELIN D, NOVIKOVA LN, WIBERG M, KELLERTH J-O, NOVIKOV LN (2009) Effects of N-acetyl-cysteine on the survival and regeneration of sural sensory neurons in adult rats. Brain Res, 1287: 58-66.

WONDRAK GT, VILLENEUVE NF, LAMORE SD, BAUSE AS, JIANG T, ZHANG DD (2010) The cinnamon-derived dietary factor cinnamic aldehyde activates the Nrf2-dependent antioxidant response in human epithelial colon cells. Molecules [Online], 15(5): 3338-3355.

WU L, XIONG X, WU X, YE Y, JIAN Z, ZHI Z, GU L (2020) Targeting oxidative stress and inflammation to prevent ischemia-reperfusion injury. Front Mol Neurosci, 13: 28.

XIE AX, TAVES S, MCCARTHY K (2022) Nuclear factor κB-COX2 pathway activation in non-myelinating Schwann cells is necessary for the maintenance of neuropathic pain in vivo. Front Cell Neurosci, 15: 782275.

YUAN X, HAN L, FU P, ZENG H, LV C, CHANG W, RUNYON RS, ISHII M, HAN L, LIU K (2018) Cinnamaldehyde accelerates wound healing by promoting angiogenesis via up-regulation of PI3K and MAPK signaling pathways. Lab Invest, 98: 783-798.

YÜCE S, GÖKÇE EC, ISKDEMIR A, KOÇ ER, CEMIL DB, GÖKÇE A, SARGON MF (2015) An experimental comparison of the effects of propolis, curcumin, and methylprednisolone on crush injuries of the sciatic nerve. Ann Plast Surg, 74: 684-692.

ZAIDMAN M, NOVAK CB, MIDHA R, DENGLER J (2024) Epidemiology of peripheral nerve and brachial plexus injuries in a trauma population. Can J Surg, 3: E261-E268.

ZENCIRCI SG, BILGIN MD, YARANERI H (2010) Electrophysiological and theoretical analysis of melatonin in peripheral nerve crush injury. J Neurosci Methods, 191: 277-282.