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# Effect of crocetin on functional recovery in the rat model of sciatic nerve crush injury: comparison with vitamin C

**Seyede Soraya Mahmoudi[1]*, Esmaeal Tamaddonfard[2], Amir Abbas Farshid[1]**

*[1] Department of Pathobiology, Faculty of Veterinary Medicine, Urmia University, Urmia, Iran; [2] Department of Basic Sciences, Faculty of Veterinary Medicine, Urmia University, Urmia, Iran.*

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## Abstract

Crocetin (CRT) is one of the active chemical compounds of saffron and has many biological effects such as antioxidant property. The present study investigated the effects of CRT on crushed sciatic nerve function. Vitamin (Vit) C was used as an antioxidant drug. Thirty rats were divided into six groups including intact, sham, crush, CRT 7.50, CRT 30.00 and Vit C 100. Nine other rats with no surgery were scheduled in three groups to receive 7.50 and 30.00 mg $kg^{-1}$ CRT and 100 mg $kg^{-1}$ Vit C. In anesthetized rats, right sciatic nerve was crushed using a small hemostatic forceps. Sciatic functional index values on days five, 10, 15 and 20 after crush were accelerated, the severities of sciatic nerve degeneration and gastrocnemius muscle atrophy were ameliorated, and the increased malondialdehyde level and the decreased superoxide dismutase activity in the serum were restored by 20 consecutive days of oral administration of 30.00 mg $kg^{-1}$ CRT and 100 mg $kg^{-1}$ Vit C. No significant differences were observed between 30.00 mg $kg^{-1}$ and 100 mg $kg^{-1}$ Vit C. The groups that did not have surgery but received CRT (7.50 and 30.00 mg $kg^{-1}$) and Vit C (100 mg $kg^{-1}$) showed no behavioral, histopathological and biochemical alterations when compared to intact group. It was concluded that CRT and Vit C produced similar improving effects on crushed-injured sciatic nerve function. Inhibition of oxidative stress, enhancement of endogenous antioxidant activity might be involved in improving effects of CRT and Vit C.



## Introduction

The peripheral nervous system is responsible for conducting sensory inputs from the peripheral organs to the brain and motor information in the opposite direction.[1] Infection, metabolic diseases, nutritional status, toxins and trauma cause neuropathy, axonopathy and myelinopathy in the peripheral nervous system.[2] Traumatic peripheral nerve injuries (PNIs) due to compression, crush and transection are important clinical and public health issues that often result in sensorimotor abnormalities.[3] Reactive oxygen species production, endogenous antioxidants reduction, inflammation and apoptosis are the major factors involving in pathophysiology of PNIs.[4,5] Despite the progressive advances using surgical methods, pharmacological and cell-based therapies, a perfect outcome with complete functional recovery has not been guaranteed.[6] Therefore, the use of medicinal plants and their biologically active substances should be seriously considered to optimize the management of peripheral nerve lesions.[7]

*Crocus sativus L.* (saffron) as a traditional herb is used for blood stasis suppression and relieving of depression.[8] Pharmacological findings have shown that the active compounds of saffron, including safranal, crocin and crocetin (CRT) have antioxidant, anti-inflammatory, anti-apoptosis, anti-diabetic and anti-cancer properties.[9] The CRT ($C_{20}H_{24}O_4$) is an aglycone of crocin and possesses antioxidative, anti-inflammatory, cardioprotective, hepato-protective, antiviral, anticancer, atherosclerotic, antidiabetic and memory-enhancing properties.[10] The CRT affects nervous system structure and function in pathological states. The CRT was found to exert rapid antidepressant effects via suppressing the expression of inflammatory cytokines and apoptotic molecules.[11] Moreover, CRT reduced neuronal apoptosis and neuro-inflammation and enhanced autophagy after traumatic brain injury in mice.[12]

There are no reports showing the effects of CRT on peripheral nerve injury outcomes. This study was planned to investigate the effects of CRT on motor disorders, histopathological and biochemical changes in the rat

***Correspondence:**

Seyede Soraya Mahmoudi. DVM, DVSc
Department of Pathobiology, Faculty of Veterinary Medicine, Urmia University, Urmia, Iran
**E-mail**: ss.mahmoudi@urmia.ac.ir

model of sciatic nerve crush injury. Sciatic functional index (SFI), sciatic nerve and gastrocnemius muscle histopathological alterations and serum malondialdehyde (MDA) level and superoxide dismutase (SOD) activity were determined. The effects of CRT were compared to vitamin (Vit) C. The Vit C, as a water-soluble Vit, has important physiologic roles in numerous metabolic functions including tissue growth and maintenance, amelioration of oxidative stress and immune regulation.[13] It has been reported that Vit C exerts neuroprotective effects against neurodegenerative diseases such as multiple sclerosis and Alzheimer's disease.[14] Moreover, Vit C was found to ameliorate cisplatin-induced peripheral neuropathy by anti-inflammatory and antioxidative effects.[15]

## Materials and Methods

**Animals.** In the current study, 48 male adult Wistar rats weighing between 200 - 220 g and aged 7 - 8 months were used. The animals were maintained under standard laboratory animal husbandry conditions (temperature: 22.00 ± 0.50 ˚C; humidity: 60.00 - 70.00% and 12 hr dark/light cycles) with free access to food and water. Behavioral tests were recorded between 10:00 AM - 3:00 PM. The study protocol was approved by Veterinary Ethics Committee of Urmia University Faculty of Veterinary Medicine (Ethical code: IR-UU-AEC-3/100).

**Chemical compounds.** The CRT and Vit C were purchased from Sigma-Aldrich, St. Louis, USA. The CRT was dissolved in Tween 80.00% (Sigma-Aldrich, Chemical Co., St. Louis, MO, USA) and diluted by normal saline and Vit C dissolved in normal saline. Drug solutions were prepared 30 min before use. All the analytical chemicals including sodium dodecyl sulphate, acetic acid, thiobarbituric acid, n-butanol, pyridine, 2,4,6-tripyridyl-S-triazine and FeCl3. 6H2O were purchased from Merck Chemical Co. (Darmstadt, Germany). Salamat Company supplied MDA, SOD assay kits (Salamat Co. Urmia, Iran).

**Study protocol.** After 15 days adaptation, the present study was conducted witihn a 25-day period. To familiarize with the experimental conditions, animals were transferred to the laboratory on days four, eight and 12 of adaptation period and subjected to SFI test. During the experimental period, on the day one, the animals underwent a surgical procedure to create a crush lesion in the sciatic nerve. The SFI was recorded on day five before and on days five, 10, 15, and 20 after surgery. On the last day of the experiment (day 20), the animals were euthanized and blood sampling was done.

**Animal grouping.** In the present study, 30 rats were divided into six groups of five rats each as follows: Group 1 (Intact)**:** This group did not undergo any kind of anesthetic, surgery or treatment. Group 2 (Sham): This group had a surgery without manipulation of the sciatic nerve and no drug treatment was used. Group 3 (Crush): In this group, a surgical crush lesion was created in the sciatic nerve and treated with vehicle (Tween 5.00 %). Group 4 (CRT 7.50): This group was treated with 7.50 mg $kg^{-1}$ CRT after surgery. Group 5 (CRT 30.00): This group was treated with 30.00 mg $kg^{-1}$ CRT after surgery. Group 6 (Vit C 100): This group was treated with 100 mg $kg^{-1}$ Vit C after surgery. Nine healthy rats were divided into three groups of three rats to receive CRT (7.50 and 30.00 mg $kg^{-1}$) and Vit C (100 mg $kg^{-1}$). The aim of this experiment was to investigate the behavioral, histopathological and biochemical effects of the tested drugs in animals without sciatic nerve crush injury. The results of this experiment were compared to the results of the intact group. The drug dosages used in the current study were consistent with other studies,[16,17] and our preliminary experiments.

**Sciatic nerve crush injury.** Sciatic nerve crush injury was induced according to the previously described method.[18,19] Briefly, by intraperitoneal injection of ketamine (80.00 mg $kg^{-1}$; Alfasan, Woerden, Netherlands) and xylazine (8.00 mg $kg^{-1}$; Alfasan) anesthesia, a 2.00-cm incision was made over the lateral aspect of the hind limb and muscles were separated in order to expose the sciatic nerve. The nerve was crushed at 2.00 cm above the trifurcation point using a small hemostatic forceps. The nerve was crushed for 60 sec with an estimated pressure of 0.50 - 1.00 kg $mm^2$. During the crash, muscle twitches and inward movements of the hind paw fingers were observed. The crushed zone was approximately 2.00 - 3.00 $mm^2$ and uniformly transparent for several minutes thereafter. The muscle layers were re-approximated using 4/0 chromic gut sutures (Supa, Tehran, Iran) and the skin was closed with 3/0 silk sutures (Supa).

**Sciatic functional index.** The SFI was carried out by obtaining footprints as previously described.[18-20] To obtain foot prints, rats were slightly restrained and their hind feet were pressed down onto a stamp pad soaked with water soluble blue ink and were immediately allowed to walk along the wooden corridor (100 × 7.50 × 25.00 cm) whose floor was covered with white paper stripes (100 × 7.50 cm). The following indicators were measured from the footprints: Print length (PL): distance from the heel to the 3rd toe, toe spread (TS): Distance from the 1st to 5th toe, and intermediary toe spread (ITS): Distance from the 2nd to the 4th toe, from the experimental (E) and normal (N) limbs. Three factors were calculated form the indicators as follows:

$$PL = (EPL - NPL)/NPL$$

$$TS = (EST - NST)/NST$$

$$ITS = (EIT - NIT)/NIT$$

The SFI was calculated by the following formula:

$$SFI = -38.30\,[(EPL - NPL)/NPL] + 109.50\,[(ETS - NTS)/NTS] + 13.30\,[(EIT - NIT)/NIT] - 8.80$$

The SFIs around 0.00 and −100 indicated normal and complete function, respectively.

**Blood and tissue sampling.** On day 20, rats were anesthetized with the anesthesia program mentioned above. Blood samples were taken directly from the heart and serum samples were obtained by blood centrifuging and stored at –20.00 ˚C for further assay. For histopathological evaluation, sciatic nerves of rats were taken out and placed in 10.00% formalin solution. Thereafter, the rats were euthanized by intracardiac injection of 1.00 mL ketamine.[21]

**Histopathological evaluation.** The formalin fixed nerves were routinely processed for paraffin embedding, thin (4.00 - 5.00 µm) transverse sections from nerves were cut and stained with Hematoxylin and Eosin for light microscopic observations. The evaluation of the sections was based on the severity of pathological changes on a scale from normal (0.00) to sever (3.00) changes.[20]

**Biochemical determination.** Serum level of MDA was determined by assay kit. In brief, the basis of MDA estimation is the reaction with thiobarbituric acid and the generation of the MDA-thiobarbituric acid adduct. This adduct can be simply quantified spectrophotometrically. The MDA levels were expressed as nmol $mL^{-1}$. Serum activity of SOD was analyzed by SOD assay kit based on the manufacture protocol. Briefly, the principle of SOD enzyme assay is inhibition of pyrogallol oxidation. This compound (pyrogallol) rapidly autoxidized in existence of molecular oxygen in an alkaline environment. As a result of the autoxidation of pyrogallol, an intermediate compound called semi-quinone radical is produced, and then pyrogallol-quinone is produced, and the last compound can be measured at 420 nm. The higher the activity of the enzyme, the less pyrogallol-quinone compound is produced. Finally, the SOD activity was expressed as U $L^{-1}$.

**Statistical analysis.** Data were analyzed using GraphPad Prism (version 8.2; GraphPad Software Inc., San Diego, USA). The time-point results obtained from SFI was analyzed using two-way repeated measures ANOVA followed by Bonferroni's *post hoc* test. The SFI averages and biochemical data were analyzed by one-way ANOVA followed by Tukey's post hoc test. Considering that microscopic scoring findings were semi-quantitative, Kruskal-Wallis and post hoc Nunn tests were used. Data are presented as mean ± SEM. A $p$ value smaller than 0.05 was considered for all results.

## Results

No significant differences were observed when CRT (7.50 and 30.00 mg $kg^{-1}$) and Vit C (100 mg $kg^{-1}$) without surgery groups were compared to intact group (data not shown). Figure 1 shows the effects of CRT and Vit C on time-point (A) and average (B) of SFI alterations induced by sciatic nerve crush injury. With no significant differences, SFI at the test days was around 0.00 in intact and sham groups. In the crush group, SFI was -114.72 ± 11.28 on day five and reached to – 82.46 ± 12.04 on day 20 after crush injury and showed significant differences ($p$ < 0.001) with intact and sham groups. The CRT (7.50 mg $kg^{-1}$) did not affect time-point SFI. The CRT (30.00 mg $kg^{-1}$) significantly increased the SFI to – 44.43 ± 5.42 ($p$ < 0.05) on day five and reached it to the intact and sham groups value (– 7.09 ± 2.68; $p$ > 0.05) on day 20. The Vit C (100 mg $kg^{-1}$) significantly increased the SFI to – 54.71 ± 6.08 ($p$ < 0.05) on day five and reached it to the intact and sham groups value (– 6.32 ± 3.13; $p$ > 0.05) on day 20 (Fig. 1A). When the average of SFI was analyzed by one-way ANOVA, a significant ($p$ < 0.0001) difference was observed between groups. Subsequent analysis by Turkey's test revealed that CRT (30.00 mg $kg^{-1}$) and Vit C (100 mg $kg^{-1}$) significantly ($p$ < 0.001) decreased the SFI, whereas, CRT (7.50 mg $kg^{-1}$) was without effect (Fig. 1B).

Figures 2A-2F show the effects of CRT and Vit C on histopathological changes in the sciatic nerve induced by crush injury. No histopathological changes were observed in intact (score: 0.00) and sham (score: 0.00) groups. Crush group showed edema, vacuolation and ellipsoid bodies (score: 2.75 ± 0.10). The CRT (7.50 mg $kg^{-1}$) had no effect (score: 2.59 ± 0.11). The CRT at a dose of 30.00 mg $kg^{-1}$ (score: 0.69 ± 0.08) and Vit C at a dose of 100 mg $kg^{-1}$ (score: 0.65 ± 0.09) significantly ($p$ < 0.05) decreased histopathological alterations (Fig. 3A).

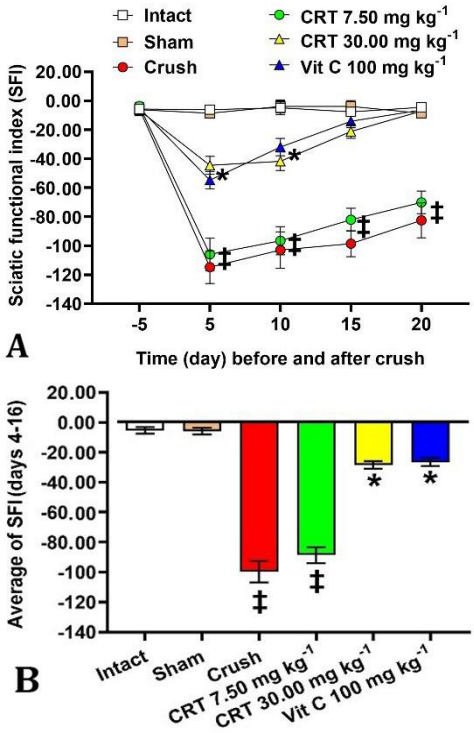


**Fig. 1.** Effects of crocetin (CRT) and vitamin (Vit) C on **A)** time-dependent and **B)** average of sciatic functional index (SFI) alteration in crushed sciatic nerve in rats. Values from each group are the mean ± SEM (n = 5). * $p$ < 0.05 and ǂ $p$ < 0.001 in comparison with intact and sham groups.

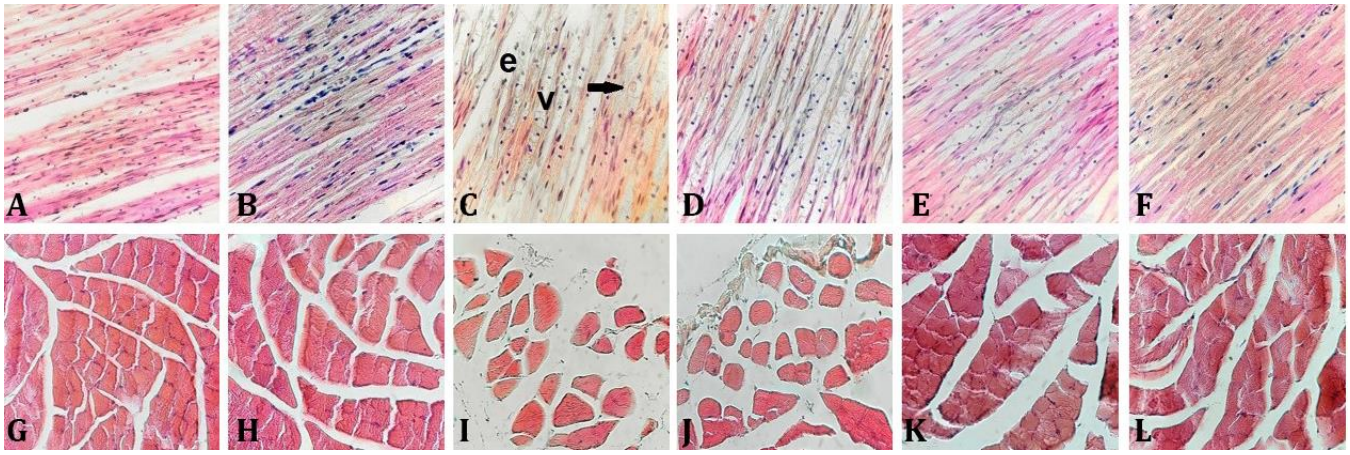


**Fig. 2.** Colored longitudinal micrographs of sciatic nerve distal segment. **A)** Intact and **B)** sham groups show normal nerve fiber architecture. **C)** Crush group shows Wallerian degeneration, indicated by edema (e), vacuolations (v), degenerated debris and ellipsoid body (black arrow). **D)** Histopathological changes of Wallerian degeneration are seen, vacuolations (V) noted in 7.50 mg $kg^{-1}$ crocetin (CRT)-treated group. **E)** and **F)** minimal histopathological changes of Wallerian degeneration are shown in 30.00 mg $kg^{-1}$ CRT and 100 mg $kg^{-1}$ vitamin (Vit) C, respectively. Colored transverse micrographs of gastrocnemius muscle. **G)** Intact and **H)** sham groups show normal nerve fiber architecture. **I)** Crush group shows myoatrophy. **J)** Muscular atrophy is seen in 7.50 mg $kg^{-1}$ crocetin (CRT)-treated group. **K)** and **L)** Minimal muscle atrophy is shown in 30.00 mg $kg^{-1}$ CRT and 100 mg $kg^{-1}$ vitamin (Vit) C, respectively (Hematoxylin and Eosin, 400 ×).

Figure 2G-2L shows the effects of CRT and Vit C on histopathological changes in the gastrocnemius muscle induced by sciatic nerve crush injury. No histopathological changes were observed in intact (score: 0.00) and sham (score: 0.00) groups.

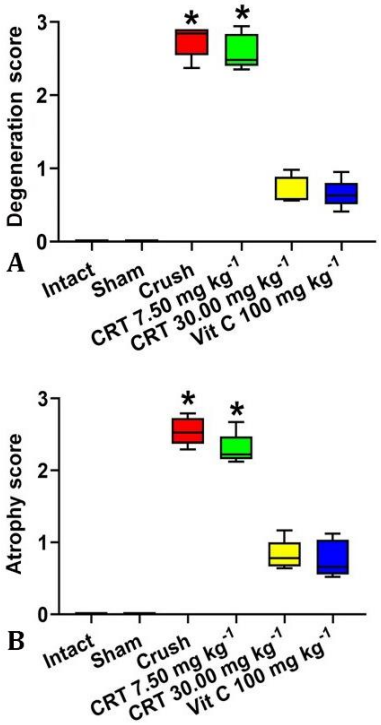


**Fig. 3.** Score of **A)** degeneration of distal segment of sciatic nerve and **B)** atrophy of gastrocnemius muscle. Data are presented as quartiles minimum value, first quartile, median, third quartiles and maximum value. Values from each group are the mean ± SEM (n = 5). * $p < 0.05$ in comparison with intact and sham groups.

Crush group showed massive muscular atrophy (score: 2.54 ± 0.09). The CRT (7.50 mg $kg^{-1}$) had no effect (score: 2.29 ± 0.10). The CRT at a dose of 30.00 mg $kg^{-1}$ (score: 0.82 ± 0.09) and Vit C at a dose of 100 mg $kg^{-1}$ (score: 0.78 ± 0.09) significantly ($p < 0.05$) decreased histopathological alterations (Fig. 3B).

Figure 4 shows the effects of CRT and Vit C on serum MDA level and SOD activity alterations induced by sciatic nerve crush injury. In intact group, MDA level and SOD activity in sciatic nerve were 0.73 ± 0.05 nmol $mL^{-1}$ (Fig. 4A) and 68.01 ± 4.31 U $L^{-1}$ (Fig. 4B), respectively. No significant differences were observed between intact and sham groups. In crush group, MDA level was significantly ($p < 0.05$) increased to 1.09 ± 0.09 nmol $mL^{-1}$ (Fig. 4A) and SOD activity was significantly ($p < 0.001$) decreased to 48.01 ± 4.04 U $L^{-1}$ (Fig. 4B) when compared to intact and sham groups. The CRT (7.50 mg $kg^{-1}$) did not alter sciatic nerve MDA level and SOD activities (Fig. 4). The increased MDA level (Fig. 4A) and the decreased SOD activity (Fig. 4B) were reversed by 30.00 mg $kg^{-1}$ CRT and reached to 0.77 ± 0.07 nmol $mL^{-1}$ ($p < 0.01$) and 66.53 ± 3.89 U $L^{-1}$ ($p < 0.05$), respectively. The Vit C (100 mg $kg^{-1}$) decreased the increased MDA level to 0.71 ± 0.06 nmol $mL^{-1}$ and increased the SOD activity to 67.79 ± 4.64 U $L^{-1}$ (Fig. 4).

## Discussion

In the present study, CRT and Vit C accelerated SFI alterations induced by crush in sciatic nerve toward normal values. Walking track analysis, known as the SFI, is a quantitative method of analyzing hind limbs performance by examining footprints and has been widely used to quantify functional recovery from sciatic nerve

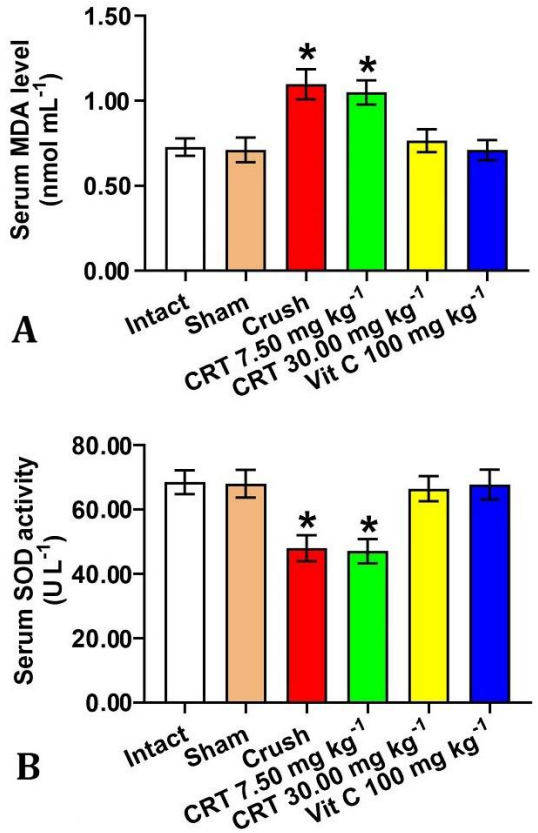


**Fig. 4.** Effects of crocetin (CRT) and vitamin (Vit) C on **A)** malondialdehyde (MDA) level and **B)** superoxide dismutase (SOD) activity in the serum of rats. Values from each group are the mean ± SEM (n = 5). * $p < 0.05$ in comparison with intact and sham groups.

crush injury model in rats.[18-20,22] Although the effect of CRT on the locomotor system has not been reported, it has improved the motor system dysfunction of 6-hydroxy-dopamine-induced hemi-Parkinsonian disease model in rats.[23] Moreover, using the Basso, Beattie, and Bresnahan assay, CRT has been found to facilitate the recovery of motor function in rats with experimentally-induced spinal cord injury.[24] Regarding the effect of Vit C on SFI, it has been reported that in chronic constriction and crush models of sciatic nerve injury, Vit C improves the functional recovery of by accelerating SFI.[25,26]

In the current study, CRT and Vit C ameliorated histopathological alteration in the nerve and atrophy in the gastrocnemius muscle. In the distal segment of crushed sciatic nerve, histopathological changes including vacuolation, degenerated debris and ellipsoid bodies and edema have been reported.[20,27] Many studies related to sciatic nerve crush injury have reported atrophy and weight loss of the gastrocnemius muscle.[19,20] Although there has been no report yet on the effect of CRT on the histopathology of sciatic nerve and gastrocnemius muscle after crush injury, other saffron compounds such as crocin and safranal have shown inhibitory effects on the formation of myelin debris and ellipsoids.[18,19] It has been reported that Vit C increases axon density and size in sciatic nerve and alleviates myopathy in gastrocnemius muscle in the mouse model of sciatic nerve crush injury.[28] Moreover, Vit C in comparison with cerebrolysin (a neurotrophic factor) and dexamethasone (an anti-inflammatory drug) produced better alleviating effects on histopathological outcomes in sciatic nerve and gastrocnemius muscle after sciatic nerve crush injury in rats.[26]

In the present study, the increased MDA levels and the decreased SOD activity in the serum of rats with sciatic nerve crush injury were restored to almost normal levels by CRT and Vit C treatments. These results were in complete agreement with previous findings in which an increase in the serum level of MDA has been reported on days 16 and 21 after induction of crush injury in the sciatic nerve.[18,19] The MDA is generated as a result of membrane lipid peroxidation and its amount is considered as a primary indicator of oxidative damage in a tissue.[29] The SOD is one of the major parts of antioxidant defense enzymatic system that regulates oxidative stress, lipid metabolism, inflammation and oxidation in all cells.[30] The rise in MDA level and the decrease in SOD activity in the blood after sciatic nerve injury may reflect the activation of oxidative stress and suppression of the endogenous antioxidant system. It has been reported that sciatic nerve crush injury produces a significant decrease in catalase and SOD activities and increase in MDA level in the sciatic nerve tissue.[27,31] Although there is no report showing the effect of CRT on blood MDA and SOD levels following sciatic nerve crush, in the spared nerve injury mouse model of neuropathic pain, CRT has been shown to relieve pain by increasing SOD levels in the sciatic nerve and spinal cord.[32] It has been reported that 21-day treatment with Vit C at a dose of 100 mg $kg^{-1}$ reduces MDA level and increases SOD activity in the nerve tissue in diabetic rats with sciatic nerve crush injury.[33] Moreover, it was found that Vit C administration in rats with sciatic nerve crush injury reduced the increased levels of MDA and increased the levels of SOD and catalase in serum and nerve tissue.[26]

The rat sciatic nerve crush injury model is one of the most commonly used models to research PNI-induced degeneration and regeneration mechanisms leading to functional impairment and recovery.[34] Crush injury to peripheral nerves causes axonal continuity to be disrupted and the process of Wallerian degeneration begins. Because the nerve connective tissue scaffold is not severed, the axonal fibers are allowed to grow and, through the regeneration process, facilitate functional recovery.[35] Oxidative stress plays a central role in the PNI degeneration and regeneration processes because it causes extensive changes in macromolecules such as DNA, proteins and lipids which leads to cell damage and death and ultimately functional impairment.[36] Suppressing

oxidative stress and the internal antioxidant system stimulation by antioxidants such as Vit s and natural products and investigating their mechanism of action could be an important aspect in the optimal management of PNI outcomes.[37,38]

The results of the present study indicated that sciatic nerve crush injury caused histopathological changes in the nerve and atrophy of the gastrocnemius muscle, leading to functional impairment by stimulating oxidative stress factors and suppressing the activity of the antioxidant system. Treatment with CRT and Vit C, by acting inversely on oxidative stress and antioxidant system, alleviated the histopathological changes and accelerated functional recovery.

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**Conflict of interest**

No financial or other conflicts of interest are declared by the authors.

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