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ORIGINAL ARTICLE

Toxic Effect of Deltamethrin on the Sciatic Nerve and the Ameliorative Effect of Ginseng in Adult Male Albino Rat (Ultrastructure and Morphometric Study)

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ABSTRACT

Background: Ginseng enhances the body's defense against harmful influences and helps restore homeostasis. Its active components are beneficial in alleviation of neurodegenerative diseases. *Aim*: To investigate the potential ameliorative impact of ginseng on sciatic nerve neuropathy caused by deltamethrin.

Methods: A total of 40 adult male rats were randomly divided into four equal groups (10 rats each): Group I served as the control group, Group II functioned as ginseng group, Group III received deltamethrin treatment, and Group IV received a combination of deltamethrin and ginseng. The experiment was conducted over a period of four weeks. At the end of the study, samples from the right sciatic nerve were collected and examined using light and electron microscopy, along with morphometric analysis.

Results: Light microscopy and morphometric studies of the deltamethrin-treated group showed a statistically significant decrease in diameter and thickness of myelin fibers, number of myelin fibers, and a non-significant reduction in axon diameter. The co-administration of ginseng with deltamethrin showed a statistically significant increase in myelinated fiber diameter, myelin sheath thickness, number of myelinated fibers, and axon diameter compared to the deltamethrin group.

The ultrastructural examination of the deltamethrin group showed extensive axonal degeneration and atrophy. Disrupted and separated myelin sheaths with dilated Schmidt-Lanterman clefts were seen. Axonal “Onion bulb" appears in some of the nerve fibers with edema of the unmyelinated nerve fiber. Edematous Schwann cell with vacuolation, and endoneurium edema. Swelling, disrupted cisterna, and vacuolation of axonal mitochondria were noticed. The co-administration of ginseng with deltamethrin has been considered a promising therapeutic approach in sciatic nerve repair and regeneration.

Conclusion: Ginseng is useful for regenerating the sciatic nerve after deltamethrin's damaging effects.

Keywords: Deltamethrin, Ginseng, Sciatic Nerve, Neuropathy, Ultrastructure, Morphometry, Rats.

INTRODUCTION

Since the 1980s, pyrethroids, which derived from pyrethrin and used to control pests in residential, veterinary, and agricultural settings, have been considered one of the most widely used synthetic pesticides. Several different kinds of pyrethroids were present in the environment, such as in the air, surface water, soil, and agricultural products [1]. According to research that was carried out in eight distinct countries [2], every person had been exposed to pyrethroids in some way during their daily lives in every region of the world. The action of pyrethroids on insect nervous systems had via disruption of voltage-gated sodium channels (VGSCs), it had been known that

various changes in VGSCs' amino acid sequence contribute to the 1000-fold difference in susceptibility to pyrethroids between both insects and mammals [3]. The effects of pyrethroids on mammals have been found to be neurotoxic according to research [4]. Deltamethrin (DM) is a type II pyrethroid with an α -cyano-3-phenoxybenzyl structure, which is widely distributed all over the world. Oxidative stress caused by DM leads to damage to several mammalian organs, including the nervous system [5]. The mechanisms of deltamethrin-induced neurotoxicity have not been fully understood; however, these findings raise considerations about exposure to deltamethrin that might be a possible risk factor for the emergence of neurodegenerative diseases.

For thousands of years, China, Korea, and Japan have practiced ginseng, which belongs to the Panax genus, Araliaceae family, as a traditional herbal remedy. Ginseng is a well-known, widely used health supplement, medicine, having a wide range of advantageous pharmacological effects. Ginseng plant components have been demonstrated to have effects on both animals, people that had adaptogenic, restorative, vasodilatory, immunomodulatory, anti-inflammatory, antioxidant, anti-aging, anti-cancer, antifatigue, antidiabetic, antistress, and anti-depressive [6].

The major problem of nervous system damage results from ischemia, inflammatory reactions, and excessive release of excitatory neurotransmitters that follow the damage [7]. After spinal cord injury (SCI), ginseng extract improved functional recovery and reduced neuronal damage, according to previous research [8]. S100 proteins, formed by a family of S100 genes [9], had 2 calcium-binding sites, amino acid sequences that were substantially conserved in vertebrates [9]. In studies on brain regeneration, S100 proteins indicate Schwann cell proliferation [10-12]. However, the role of ginseng, S100 proteins in peripheral nerve healing after injury had little understood.

So the current work was designed to evaluate the potential role of ginseng in regeneration responses to deltamethrin-induced sciatic nerve injuries in adult male rats.

METHODS

Animals:

In the current study, forty adult male albino rats weighing 200±10 g were used. They were acclimated for 7 days before the beginning of the experiment. Five rats were housed per cage in stainless steel cages in a room that was adequately aired and kept at room temperature. They received a normal laboratory pelleted meal and water as needed, while being kept on a 12-hour light/dark cycle. The study protocol was reviewed and approved by the Research Ethics Committee of the Faculty of Medicine, Suez Canal University, Egypt, (Approval No 5134#). The study followed the National Institutes of Health's guidelines for the handling, use of laboratory animals (NIH Publications No. 85-23, revised 1996). All possible measures have been taken to reduce animal suffering to the utmost extent possible.

Drugs:

Deltamethrin (>99% pure) was obtained from KZ pesticide company (Egypt).

Ginseng: 120 ml Syrup. Each 10 ml contains ginseng extract, 93.3 mg obtained from Pharco Pharmaceuticals Co. (Alexandria, Egypt).

Experimental design:

The rats were divided randomly into 4 groups, each included 10 rats.

(1) Group I (Control group): animals received 1 ml of olive oil daily by intragastric tube for 5 days.

(2) Group II (Ginseng group): animals received ginseng 20 mg/kg body weight daily by intragastric tube for 5 days [13].

(3) Group III (Deltamethrin group): animals had given deltamethrin in a daily dose of 30 mg/kg BW (1/5 LD_{50}) dissolved in 1 ml olive oil by oral gavage for 5 successive days [14].

(4) Group IV (Deltamethrin+Ginseng): The rat received ginseng 1 h before administration of deltamethrin, at the same dose as groups II, III.

Histological evaluation:

At the end of the experiment (24 hours after the last dosage of DM), the rats were anesthetized by intraperitoneal injection of 60 mg/kg ketamine, 5 mg/kg xylazine. The right

sciatic nerve was exposed, dissected, then cut into 2 specimens for immunohistochemical and electron microscopic examinations.

a- Nerve Specimen Preparation for Immunohistochemical Examination

The right sciatic nerve specimens were immediately immersed in 10% neutral buffered formalin for 24–48 hours at room temperature to ensure proper fixation. Following fixation, the specimens were rinsed in running tap water, dehydrated in ascending grades of ethanol (70%, 80%, 90%, 95%, and absolute alcohol), cleared in xylene, and embedded in paraffin wax using a standard protocol. Paraffin-embedded nerve tissues were sectioned at 4 µm thickness using a microtome and mounted on positive charged glass slides. The Paraffin-embedded nerve sections were deparaffinized in xylene, rehydrated through descending grades of ethanol solutions then incubated in 3% hydrogen peroxide (H_2O_2) for 10 minutes to block endogenous peroxidase activity. Antigen retrieval was then performed by boiling the sections in 0.01 mol/L sodium citrate buffer (pH 6.0) for 10 minutes. After cooling, the sections were incubated with normal goat serum for 15 minutes at room temperature to block non-specific binding, followed by washing with phosphate-buffered saline containing 0.1% Tween-20 (PBST, pH 7.4). The sections were then incubated overnight at 4°C with anti-S100 primary antibody (mouse monoclonal IgG2a, clone 4C4.9, GeneTex, USA). After washing, biotinylated goat anti-mouse IgG secondary antibody was applied for 20 minutes at 37°C. Subsequently, the sections were treated with streptavidin–horseradish peroxidase complex for another 20 minutes at 37°C. Color development was performed using 3,3'-diaminobenzidine (DAB) as the chromogen (Jiancheng Bioengineering Institute, Nanjing, China), and brown staining was interpreted as a positive immunoreaction.

b- Nerve specimen preparation for Electron Microscopic examination:

The other nerve specimens were fixed in 2.5% phosphate-buffered glutaraldehyde (pH 7.4) for 2 hours at 4°C before being postfixed in newly prepared 1% phosphate buffer osmium tetroxide at 4°C for 1 hour. Following that, the nerve specimens were washed twice with phosphate buffer for 30 minutes, dehydrated in ascending grades of ethanol. To generate cross-sections, nerve samples had orientated longitudinally in a flat mold, embedded in epoxy resin. Semi-thin sections were stained with toluidine blue; examined, photographed by an Olympus BX-50 light microscope with digital camera, and other ultra-thin sections had contrasted with both uranyl acetate and lead citrate [16]. The ultra-thin sections had examined and photographed by using a transmission electron microscope (JOEL-1010, Japan) in the Transmission Electron Microscope unit, at the center of Biotechnology, Mycology, Al-Azhar University, Cairo.

Histomorphometry measurements:

Histomorphometric Analysis was performed on toluidine blue-stained semithin sections obtained from the sciatic nerve embedded in epoxy resin. From each rat, three representative cross-sections of the nerve were selected. These sections were chosen to ensure consistency and avoid overlapping in counting fields. Thus, for each group (10 rats), a total of 30 sections per group were analyzed (3 sections × 10 rats). Morphometric parameters including axon diameter, myelinated fiber diameter, myelin sheath thickness, g-ratio, and number of myelinated fibers were measured in a fascicle by using a light microscope under 1000× magnification, with digital image analysis software (ImageJ). The g-ratio was calculated as the ratio of axon diameter to the total fiber diameter, which reflects the degree of myelination.

The Fiji-image J software program was used to measure the diameter of both axon (d), and nerve fiber (D).

Calculation of the myelin thickness had carried out by using the following equation (m = [D-d]/2), calculation of the g-ratio was carried out by using the following equation (d/D-ratio) [17, 18]. The g-ratio is defined as the ratio of the axon diameter to the total diameter of the myelinated nerve fiber (axon + myelin sheath) and is used to assess the degree of myelination. The number of myelinated fibers/mm² was estimated using the independent counting method within a

defined square area of 1 mm², as described by Gundersen et al. (1988) [19].

Statistical analysis:

SPSS. V 24 was used to conduct a statistical analysis on the study groups' histomorphometry data, which were displayed as means & SD. ANOVA test with Bonferroni Post Hoc Test was used to compare the study groups: P< 0.05 is considered significant.

RESULTS

1. General observation:

Throughout the experiment, no mortality or noticeable changes in appearance or behavior were observed in any of the rats across all groups. The control and ginseng groups showed consistent histological and morphometric features with no significant variations.

2. Light microscopic results:

Toluidine blue-stained semithin sections of the right sciatic nerve from the control and ginseng groups showed normal nerve architecture. The nerve fibers appeared densely packed with minimal endoneurial spaces. Myelinated fibers had compact, regular sheaths with minimal enfolding. Schwann cell cytoplasm was seen surrounding the axons, and unmyelinated fibers appeared as ovoid clusters between the myelinated fibers (Fig. 1A, 1B). In the deltamethrin-treated group, marked abnormalities were observed. These included nerve fiber dissociation, endoneurial edema, axonal degeneration, and irregular myelin sheaths. Myelin outfolding into Schwann cell cytoplasm and infolding into the axoplasm were noted. The myelin boundaries were indistinct, and compaction was deranged (Fig. 1C). The deltamethrin + ginseng-treated group showed clear improvement. Most myelinated fibers appeared with compact and regular sheaths. However, a few irregular fibers were still observed (Fig. 1D).

3. Electron microscopic results:

In the control and ginseng groups, ultrastructural examination revealed myelinated nerve fibers of varying sizes surrounded by compact, regular myelin sheaths of uniform thickness. Schwann cells displayed large euchromatic nuclei and thin cytoplasm. Clusters of unmyelinated nerve fibers were embedded within Schwann cell processes. The Schmidt-Lanterman clefts appeared narrow. The axoplasm was homogeneous, containing normal mitochondria, microtubules, and microfilaments. Schwann cells, collagen fibers, and endoneurial components appeared intact and normal (Fig. 2A–D). The deltamethrin-treated group showed marked pathological changes. These included extensive axonal degeneration and atrophy of the myelinated fibers. Many fibers exhibited disrupted and separated myelin sheaths with dilated Schmidt-Lanterman clefts. “Onion bulb” formations—concentric layers of Schwann cell processes with collagen—were observed around some axons. Edema was evident in the unmyelinated nerve fibers. Mitochondria showed swelling, disrupted cristae, and vacuolation. Endoneurial edema and vacuolated Schwann cells were also noted (Fig. 3A–D). The deltamethrin + ginseng-treated group demonstrated notable improvement. Myelinated nerve fibers appeared in various sizes with compact, regular myelin sheaths and narrow Schmidt-Lanterman clefts. Schwann cells with euchromatic nuclei were seen surrounding these fibers. Unmyelinated nerve fibers and collagen fibers were also observed in the endoneurium. The axoplasm contained normal-appearing mitochondria (Fig. 4A, B).

4. Immunohistochemical results:

Immunohistochemical staining for S100 protein was performed to evaluate Schwann cell distribution and activity in sciatic nerve tissue. The control group showed moderate, uniform S100 expression in Schwann cells lining the myelinated nerve fibers. Similarly, the ginseng‒group showed a comparable pattern of moderate S100 positivity, indicating normal Schwann cell activity (Fig. 5A, 5B). The deltamethrin-treated group exhibited markedly reduced S100 expression, reflecting a decrease in Schwann cell number and/or function due to neurotoxic damage (Fig. 5C).

In contrast, the deltamethrin + ginseng-treated group showed the highest S100 expression, with intense immunoreactivity in numerous Schwann cells, suggesting a regenerative or

protective effect of ginseng on nerve tissue (Fig. 5D).

5. Histomorphometry results:

Stereological analysis of sciatic nerve fibers morphometric parameters in a fascicle, including number of myelinated nerve fibers, diameters of myelinated nerve fibers and their corresponding axons were measured. Additionally, myelin sheath thickness, and g ratio were calculated (Table 1). Myelinated fiber diameter was significantly reduced by administration of deltamethrin in the Deltamethrin-treated group in comparison to the control group and the Ginseng-treated group. The co-administration of ginseng with deltamethrin in the Deltamethrin+Ginseng treated group showed a statistically critical increase in myelinated fiber diameter, compared to Deltamethrin treated group, also, the myelin fiber diameter in Deltamethrin+Ginseng-treated group had approximated to that in the control group (Table 1).

As regards the axon diameter, the administration of deltamethrin in Deltamethrin-treated group resulted in a critical decrease in axon diameter compared to, control group, Ginseng-treated group, Deltamethrin+Ginseng-treated group. The co-administration of ginseng with deltamethrin in the Deltamethrin+Ginseng-treated group showed a statistically significant increase in axon diameter, compared to the deltamethrin-treated group. Also, the axon diameter in the Deltamethrin+Ginseng-treated group was approximated to that in the control group (Table 1).

As regards the myelin thickness, the administration of deltamethrin in the Deltamethrin-treated group resulted in a critical decrease in myelin thickness compared to both the control group Ginseng-treated group. The co-administration of ginseng with deltamethrin in Deltamethrin+Ginseng-treated group resulted in a statistically critical increase in myelin thickness, compared to Deltamethrin-treated group, also, the values of myelin thickness in Deltamethrin+Ginseng-treated group had approximated to that in the control group (Table 1).

As regards the g ratio, all the study groups showed similar results, which indicate that the decrease in the myelinated fiber diameter, axon diameter, and myelin thickness were homogenous in the Deltamethrin group, and the increase in these parameters in the Deltamethrin+Ginseng treated group also were homogenous (Table 1).

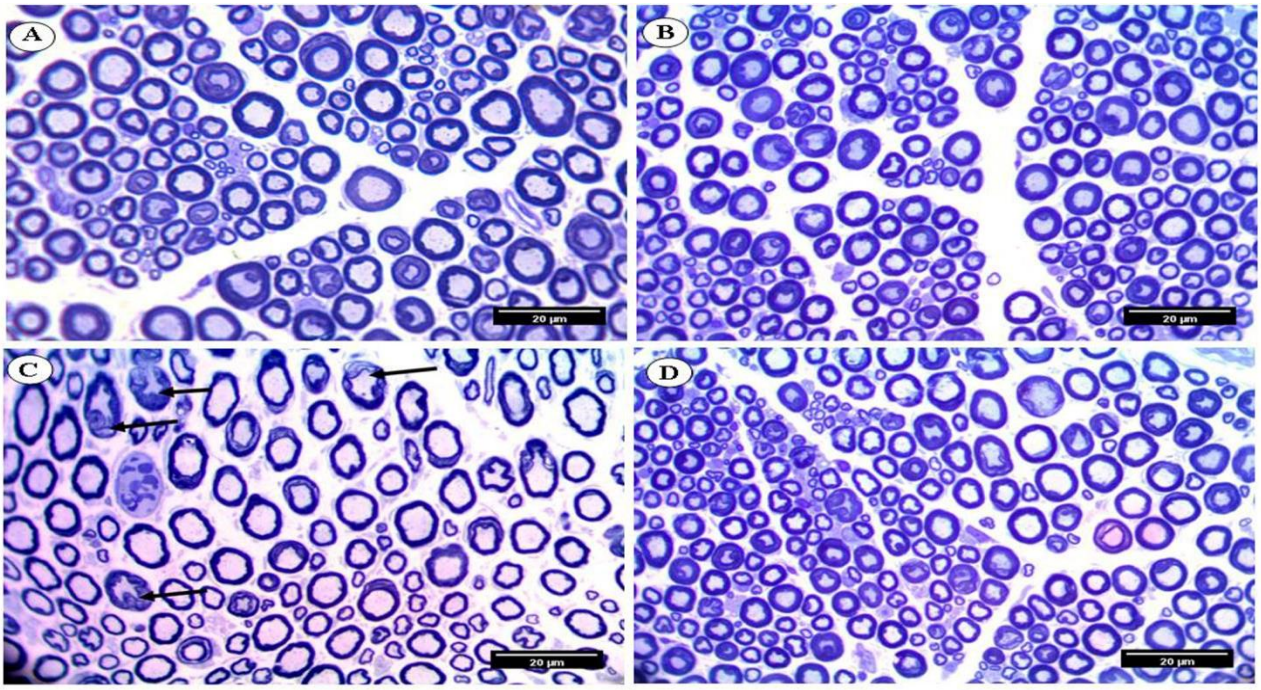
As regards the number of Myelinated fibers, the administration of deltamethrin in Deltamethrin group resulted in a critical decrease in the number of myelinated fibers compared to both control group, and Ginseng treated group. The co-administration of ginseng with deltamethrin group resulted in a statistically critical increase in number myelin fiber, by a percentage of 38.8% compared to Deltamethrin-treated group, meanwhile still there was a critical decrease in the number of myelinated fibers in Deltamethrin+Ginseng-treated group when compared to both, control, Ginseng- treated groups (Table 1).

As for the g-ratio, the Deltamethrin-treated group exhibited a noticeable reduction compared to the Control and Ginseng-treated groups, indicating thinner myelin relative to axon size. In contrast, the Deltamethrin + Ginseng group showed a marked improvement, with g-ratio values approaching those of the Control group. These results suggest that ginseng co-treatment helped restore the balance between axon and myelin thickness, contributing to functional nerve recovery (Table 1).

Table 1: Effect of Deltamethrin and Ginseng on Histomorphometric parameters of the Sciatic Nerve

	Control	Deltamethrin	Ginseng	Deltamethrin + Ginseng	F	p-value
Diameter of myelinated nerve fibers (µm)	10.58 ± 2.11	9.42 ± 2.81[a,b,c]	10.56 ± 2.43	10.36 ± 2.46	53.232	0.000
Axon Diameter (µm)	7.03 ± 1.72	6.23± 2.42[a,b,c]	7.05 ± 1.75	6.97 ± 1.82	37.109	0.000
Myelin Thickness (µm)	1.77 ± 0.68	1.59 ± 0.37[a,b,c]	1.76 ± 0.65	1.7 ± 0.59	29.216	0.000
g ratio (axon diameter / fiber diameter)	0.665 ± 0.099	0.661 ± 0.089	0.667 ± 0.087	0.673 ± 0.071	0.202	0.895
No. of Myelinated nerve fibers (at magnification 1000 x)	109.88 ± 20.52	67.25 ± 17.86[a,b,c]	109.5 ± 19.96	98.38 ± 19.57[a,b]	368.146	0.000

The data are expressed as Mean±SD. Significance of differences among groups was evaluated by one-way ANOVA followed by Bonferroni Post Hoc Test. The level of significance refers to the value of $p<0.05$.
a. significant vs. Control group b. significant vs. Ginseng group c. significant vs. Deltamethrin+Ginsing group



nerve of: **(A)** Control and **(B)** Ginseng treated groups showing myelinated nerve fibers of various size with compact regular myelin sheaths having darkly stained rounded or elliptical shapes. **(C)** Deltamethrin-treated group showing various abnormalities of myelinated nerve fibers (arrow), including irregular fiber shapes, myelin infoldings, outfoldings, alteration in myelin compaction. **(D)** Deltamethrin+Ginseng treated group showing myelinated nerve fibers of various size having compact regular myelin sheaths. Some irregularly myelinated nerve fibers had also been seen (Toluidine blue x 1000).

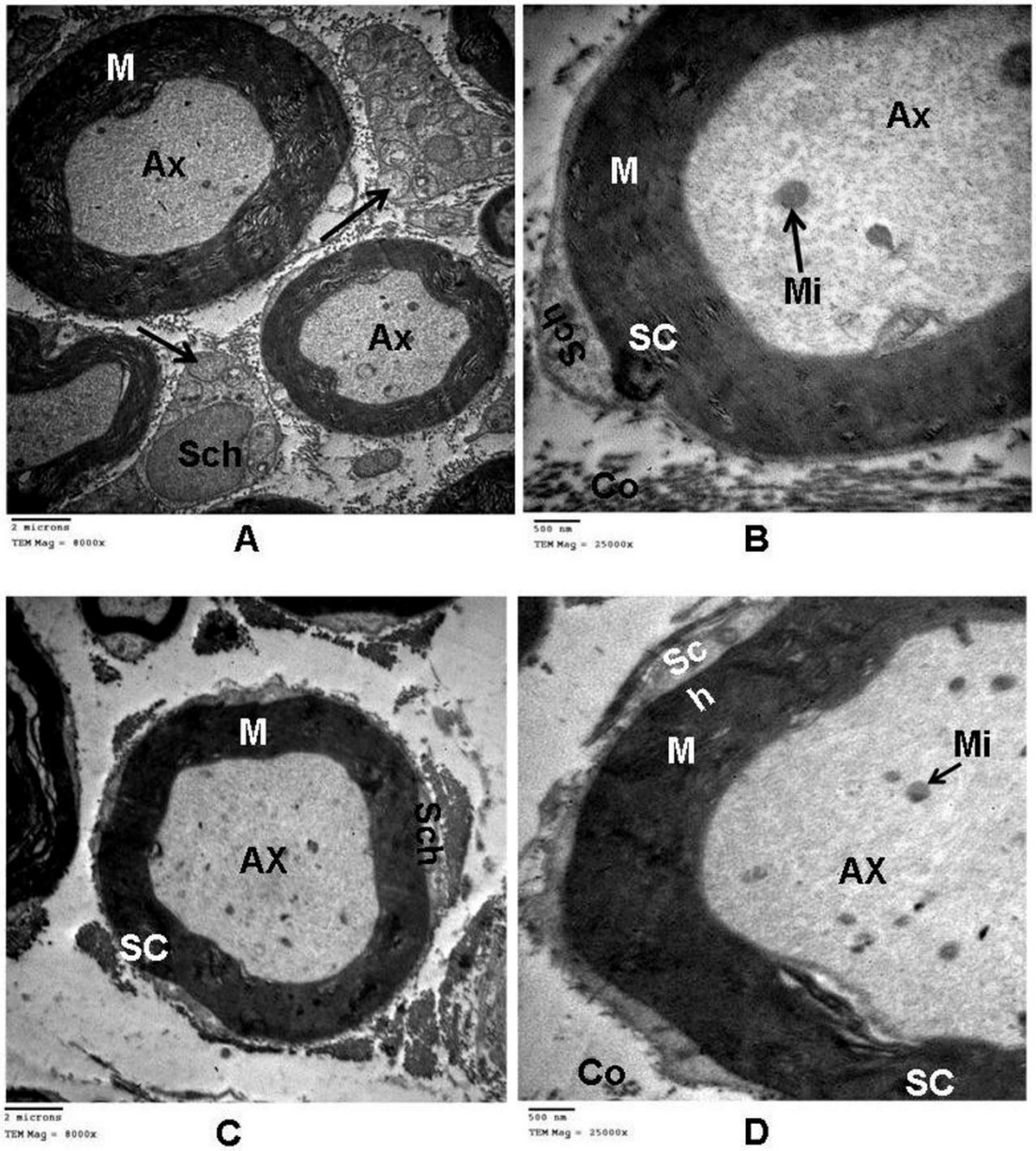


Figure 2: Transmission electron micrographs of the sciatic nerve of: **(A)** Control, and **(C)** Ginseng groups showing myelinated nerve fibers of different sizes with regular, compact myelin sheaths (M) surrounding their axoplasm (Ax). Schwann cells (Sch), with their euchromatic nuclei. Groups of unmyelinated nerve fibers (arrow) embedded in Schwann cell processes have also been seen (TEM x8000). **(B)** Control, and **(D)** Ginseng groups showing myelinated nerve fibers (M) with narrow Schmidt-Lanterman clefts (SC) in the myelin sheaths (M), along with homogenous axoplasm (Ax), with normal mitochondria (Mi). Schwann cells surrounding myelinated nerve fiber (sch), collagen fibers (co) in endoneurium have also been seen (TEM x 25000). Scale Bar = 2 microns (**A & C**), 500 nm (**B & D**).

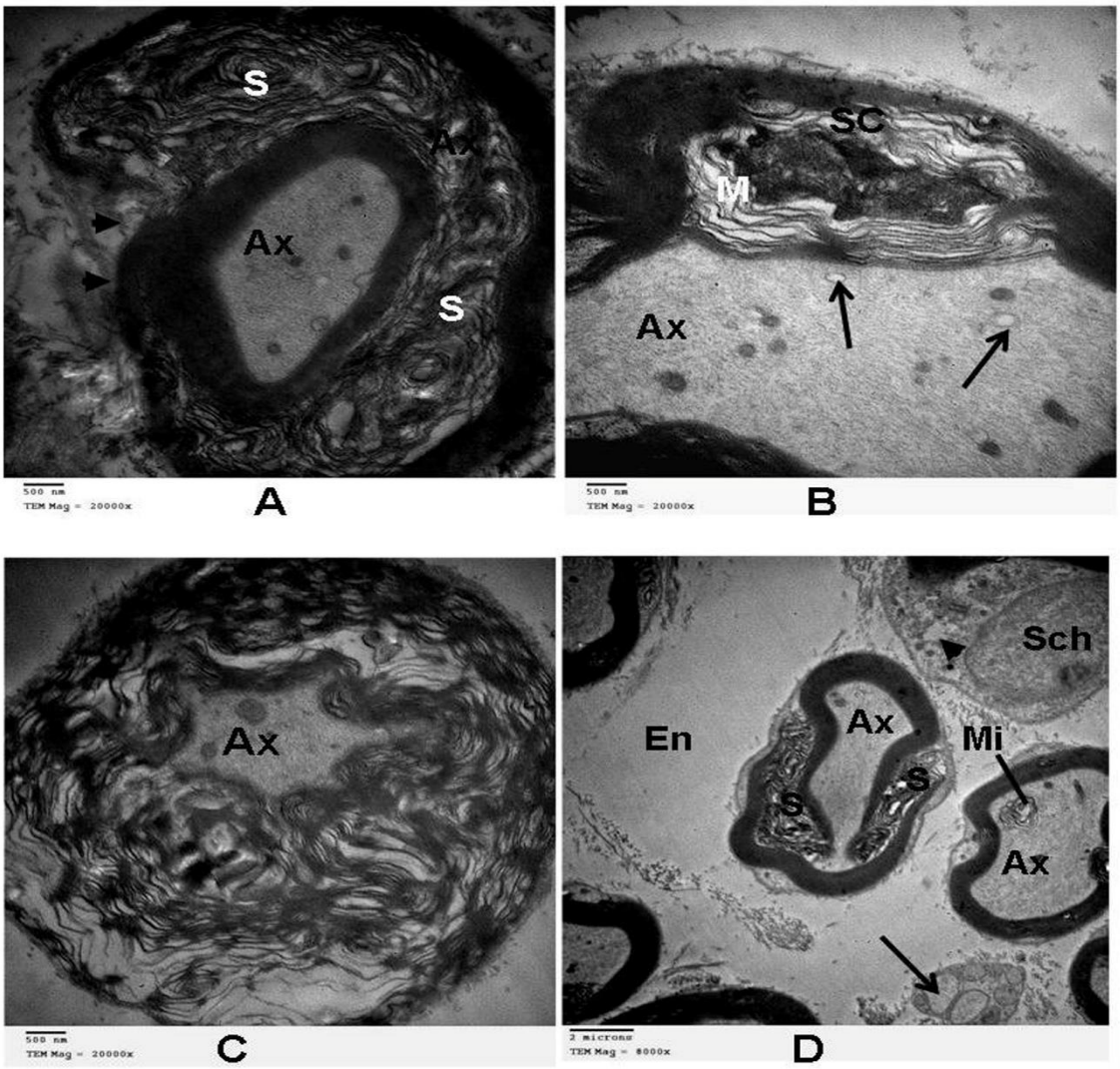


Figure 3: Transmission electron micrographs of the sciatic nerve in Deltamethrin treated group, showing **(A)** shrinkage of axoplasm (Ax), extensive degenerations of myelin sheath (arrowhead), separation of its fiber (S) (TEM x 20000). **(B)** disrupted, Separation of myelin sheath with dilated Schmidt-Lanterman Clefts (SC), vacuolated mitochondria (arrow) (TEM x 20000) **(C)** shrinkage of central axon (Ax). "Onion bulb" appeared as circular layers of Schwann cell processes, collagen around the axon in some nerve fibers (TEM x 20000). **(D)** shrinkages of axoplasm (Ax), disrupted, separation of myelin sheath, swelling of axonal mitochondria with disrupted cisterna (Mi), edematous Schwann cell (Sch) with vacuolation (arrowhead), edema of unmyelinated nerve fiber (arrow), endoneurium edema (En) (TEM x 8000).

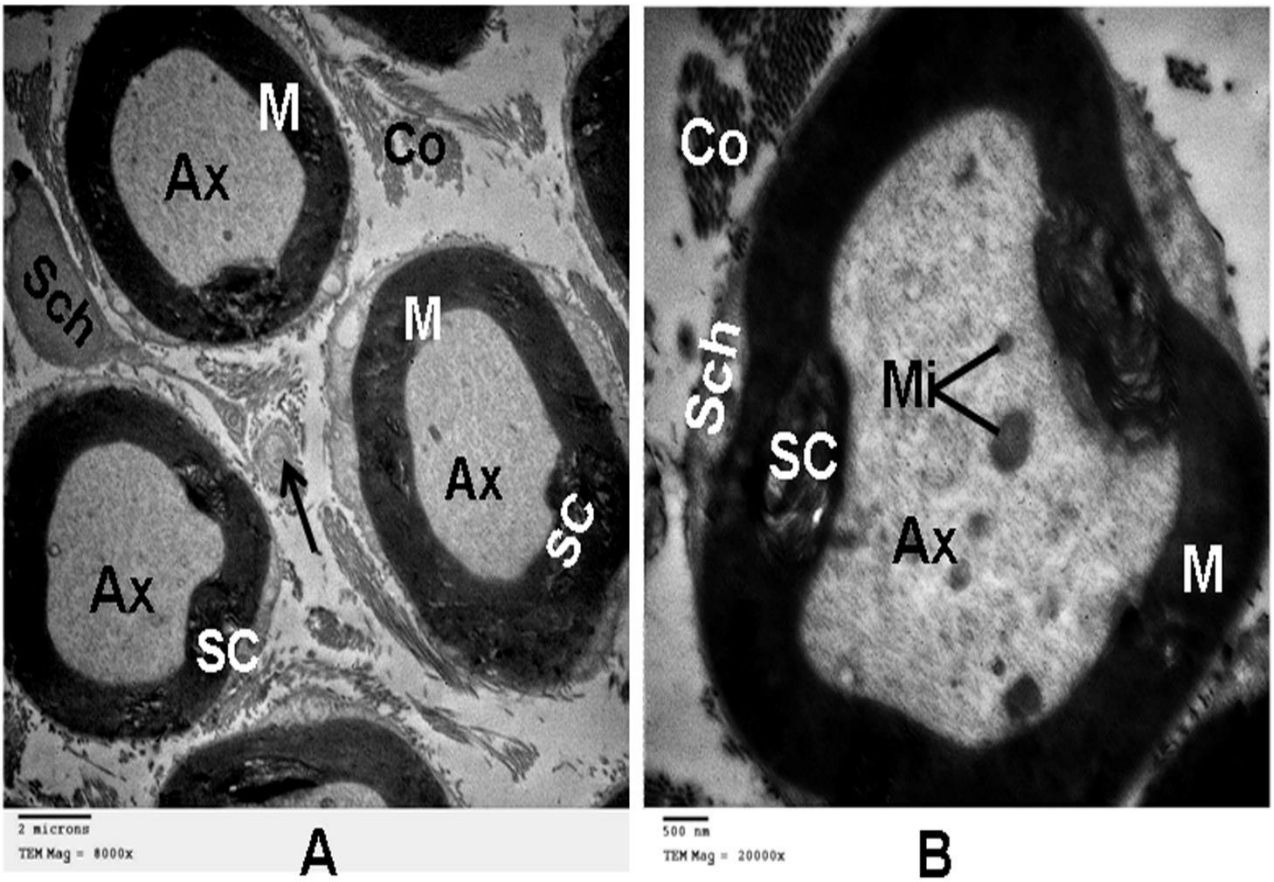


Figure 4: Transmission electron micrographs of the sciatic nerve in Deltamethrin+Ginseng-treated group, showing **(A)** myelinated nerve fibers of different sizes with regular, compact myelin sheaths (M) surrounding their axoplasm (Ax). Schwann cell (Sch), with its euchromatic nuclei. Unmyelinated nerve fibers (arrow) had also seen, collagen fibers (Co) (TEM x 8000). **(B)** myelinated nerve fibers (M) with narrow Schmidt-Lanterman Clefts (SC) contain homogenous Axoplasm (Ax), containing normal mitochondria (Mi). Schwann cells surrounding a myelinated nerve fiber (sch). Collagen fibers (co) in endoneurium have also been seen. (TEM x 20000).

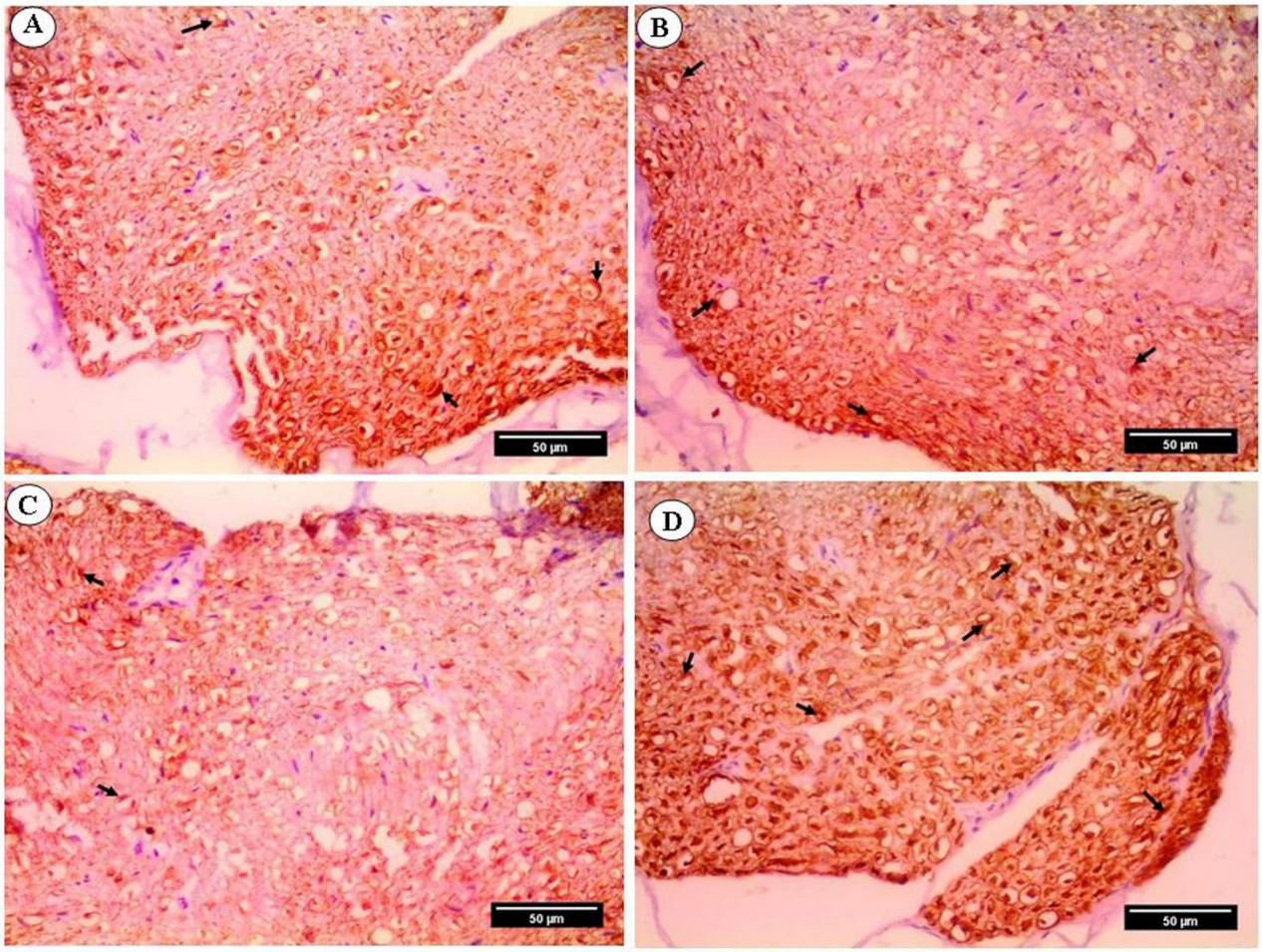


Figure 5: Photomicrographs of Immunohistochemically S-100-stained sections of sciatic nerves, arrows indicate Schwann cells that are positively stained for S100 protein, **(A)** control group shows mild expression of S-100. **(B)** Ginseng-treated group shows mild expression of S-100. **(C)** Deltamethrin-treated group displays weak expression of S-100. **(D)** Deltamethrin+Ginseng treated group shows moderate expression of S-100. (Scale bar: 50 µm).

DISCUSSION

In the present experimental study, the histopathological examination of the deltamethrin group revealed morphological changes of the degenerating sciatic nerve. These degenerative changes include endoneurial edema, nerve fiber dissociation, also, degeneration, irregularity, infoldings, and outflowing of the nerve fibers when compared to the control group. Also, there were derangements in myelin compaction, and an unclear boundary in myelin sheaths compared to the control. The ultrastructural examination showed extensive axonal degeneration and atrophy. Some nerve fibers were disrupted, separated myelin sheaths with dilated Schmidt-Lanterman clefts. “Onion bulb" appeared as circular layers of Schwann cell processes, collagen around the axon in some nerve fibers, with edema of the unmyelinated nerve fiber. Swelling, disrupted cisterna, vacuolation of mitochondria. Edematous Schwann cell with vacuolation, endoneurium edema. Confirmation of the above-mentioned deteriorating changes appearing in the sciatic nerve of this group were achieved by the results of the morphometric measurements, which showed a statistically critical decrease in both myelin fiber diameter, thickness, number of myelin fibers, meanwhile there had a noncritical decrease in axon diameter compared to both control and ginseng groups.

Another study found that rats exposed to a high dose of deltamethrin caused minor nerve damage in the form of axonal injury and changes in the myelin sheath. The thin myelin sheath's degeneration, vacuolization of the

cytoplasm, and altered Schwann cells were caused by proliferation, enlargement of the rough and smooth endoplasmic reticulum, and alterations to the Schwann cells [20].

Axonal injury and myelin sheath alterations observed in our study are supported by findings from previous research by Calore et al. (2000) [20], which similarly reported signs of Wallerian degeneration, including swollen and disrupted myelinated nerve fibers, axoplasm containing myelin fragments, and increased numbers of degenerated myelinated fibers. That study also documented a significant increase in the cross-sectional diameter of the sciatic nerve, accompanied by hyalinization, vacuolations, and patchy fragmentation of the myelin sheath findings that align closely with our observations. Some myelin sheaths appeared split or partially lost, which the authors attributed to edema-induced separation of myelin layers [21].

Additionally, our results are consistent with those of Kamel et al. (2011) [21], who reported axoplasmic vacuolization, fragmentation, shrinkage, and intra-axonal gaps, likely related to fluid accumulation and tissue edema. Swollen mitochondria with disrupted cristae were also observed in both studies, indicating mitochondrial damage. Moreover, membrane-bound, electron-dense bodies and multiple variably sized cytoplasmic vacuoles were noted within swollen Schwann cells, possibly reflecting dilatation of membrane-bound organelles, as previously suggested [21].

These structural abnormalities may be explained, at least in part, by the known effects of deltamethrin in promoting oxidative stress. It has been shown to activating p66Shc, a key regulator of reactive oxygen species (ROS) generation, in both tissue models and cell lines. Further studies confirmed that p66Shc mediates deltamethrin-induced oxidative damage in vitro, suggesting a possible mechanism for the neurotoxic effects observed in vivo [22].

There have been numerous proposed explanations for the neurotoxic effects of pyrethroid insecticides. Type I pyrethroids bind nerve membranes' sodium channels, leading to rhythmic neuronal discharge, persistent negative after potential. The presynaptic nerve terminals had the most sensitive sites. Type II pyrethroids cause an incidence-dependent, constant depolarization and conduction block in the axons of sensory and motor nerve fibers [23]. Longstanding exposure to pyrethroids could negatively affect the CNS with deterioration of neurocognitive performance [24].

Our findings showed that the co-administration of ginseng with deltamethrin in the Deltamethrin+Ginseng group showed a statistically noncritical increase in myelin fiber diameter, thickness, number of myelin fibers, and axon diameter compared to the Deltamethrin-treated group, meanwhile Deltamethrin+Ginseng group is still less than the control group. The histopathological results revealed great improvement, a picture near to the control group. The myelinated nerve fibers appeared in various sizes, having compact, regular myelin sheaths. A few irregularly myelinated nerve fibers were still present. In normal myelinated nerve fibers, mitochondria had been seen. These results agreed with another study by Liao et al. (2002) [25] about the protective effects of ginseng. Additionally, El-Derieny et al. [13] concluded that ginseng reduced the negative impact that acrylamide had on the structure of peripheral nerves.

Schwann cell population increased critically by ginseng administration in the damaged sciatic nerve. Ginseng administration enhanced proliferation, Cdc2 protein signals in Schwann cell cultures [26]. Schwann cells were essential in the injured area; their proliferation, followed by axon myelination, were essential for regeneration. Schwann cells that are proliferating not only guide axonal expansion toward the initial target, but they also remove deteriorating axonal debris from the distal end of the axons [27]. When it comes to axonal regeneration, ginsenoside Rb1 has been shown to be useful for the regeneration of peripheral axons; Rg1 has been found to be effective in facilitating the regeneration of peripheral nerves; and Schwann cells have been found to proliferate [28].

Ginseng is known for its neuroprotective properties in various neurological conditions. It has been shown to exert beneficial effects

in neurodegenerative disorders such as Alzheimer's and Parkinson's disease, and in models of neural injury, including spinal cord damage and peripheral nerve trauma [28]. These findings support the current study's results, where ginseng co-administration with deltamethrin improved structural integrity of sciatic nerve fibers and enhanced axonal regeneration.

Multiple studies have been carried out to evaluate the possible protective role of ginseng in the injured spinal cord, peripheral neurons. Ginseng improved cell migration activity had mediated by the F.G.F–2uPA–M.M.P-9 migration pathway. The corresponding pathway concerns had been interpreted by specific pathway inhibitors. These data imply the potential value of Rg1 to promote neuron regeneration, demonstrating neuroprotective effects, both lowering the degree of damage and promoting nerve fiber repair [29,30]. Schwann cells, which are glial cells found in the peripheral nervous system, have raised serious concerns regarding their potential use in the engineering of neural tissue. Schwann cells produce bio-activating chemicals that promote axonal outgrowth, and movement. Schwann cells quickened nerve cell regeneration in the case of massive nerve gap lesions [31]. Ginseng has been found to improve the cultured Schwann cell proliferation, migration in the case of peripheral nerve injuries [32]. Ginseng also improved healing, restoration of sciatic nerve injury, renovated the conductivity of recovering fibers of limb motor function, and avoided skeletal muscle wasting [33,34].

In the current study, we measured S100 expression levels to investigate the molecular basis for ginseng-induced enhancement of sciatic nerve regeneration. Immunohistochemistry had revealed that the sciatic nerve tissue expressed S100. Proliferating Schwann cells induced prolonged regeneration, which was associated with functional repair of the injured sciatic nerves [10-12]. S100 protein expression in Schwann cells has been used as an indicator for the regeneration of sciatic nerve injury induced by deltamethrin after using ginseng. It had been stated that ginsenoside highly increases S100 expression in Schwann cells to enhance the regeneration of the rat injured sciatic nerve [10]. In the current study, co-administration of ginseng with deltamethrin induced S100 immunoreactivity in Schwann cells; the Schwann cells induced improvement of the degenerative changes in myelin structure, as well as functional sciatic nerve recovery.

From our findings, the previous reviews, it seems that Ginseng has a promising therapeutic factor in nerve repair and regeneration.

Conflict of interest: None

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REFERENCE

1. Hirano T, Suzuki N, Ikenaka Y, Hoshi N, Tabuchi Y. Neurotoxicity of a pyrethroid pesticide deltamethrin had associated with the imbalance in proteolytic systems caused by mitophagy activation, proteasome inhibition. *Toxicol Appl Pharmacol*. Nov 1 2021;430:115723. doi:10.1016/j.taap.2021.115723

2. Li AJ, Kannan K. Urinary concentrations, profiles of organophosphate, pyrethroid pesticide metabolites, phenoxyacid herbicides in populations in eight countries. *Environment International*. 2018/12/01/ 2018;121:1148-54. doi:https://doi.org/10.1016/j.envint.2018.10.033

3. Field LM, Emyr Davies TG, O'Reilly AO, Williamson MS, Wallace BA. Voltage-gated sodium channels as targets for pyrethroid insecticides. *European Biophysics Journal*. 2017/10/01 2017;46(7):675-9. doi:10.1007/s00249-016-1195-1

4. Richardson JR, Fitsanakis V, Westerink RHS, Kanthasamy AG. Neurotoxicity of pesticides. *Acta Neuropathologica*. 2019/09/01 2019;138(3):343-62. doi:10.1007/s00401-019-02033-9

5. Lu Q, Sun Y, Ares I, et al. Deltamethrin toxicity: A review of oxidative stress, metabolism. *Environmental Research*. 2019/03/01/ 2019;170:260-81. doi:https://doi.org/10.1016/j.envres.2018.12.045

6. Rokot NT, Kairupan TS, Cheng KC, et al. A Role of Ginseng, Its Constituents in the Treatment of Central Nervous System Disorders. *Evid Based Complement Alternat Med*. 2016;2016:2614742. doi:10.1155/2016/2614742

7. Oyinbo CA. Secondary injury mechanisms in traumatic spinal cord injury: a nugget of this

multiple cascade. *Acta Neurobiol Exp (Wars)*. 2011;71(2):281-99.
8. Kim YO, Kim Y, Lee K, et al. Panax ginseng improves functional recovery after contusive spinal cord injury by regulating the inflammatory response in rats: an in vivo study. *Evidence-Based Complementary, Alternative Medicine*. 2015;2015:817096. doi:10.1155/2015/817096
9. Marenholz I, Heizmann CW, Fritz G. S100 proteins in mouse, man: from evolution to function, pathology (including an update of the nomenclature). *Biochem Biophys Res Commun*. Oct 1 2004;322(4):1111-22. doi:10.1016/j.bbrc.2004.07.096
10. Wang L, Yuan D, Zhang D, et al. Ginsenoside Re Promotes Nerve Regeneration by Facilitating the Proliferation, Differentiation, Migration of Schwann Cells via the ERK-, JNK-Dependent Pathway in Rat
Model of Sciatic Nerve Crush Injury. *Cellular, molecular neurobiology*. Aug 2015;35(6):827-40. doi:10.1007/s10571-015-0177-7
11. Wu SH, Huang SH, Cheng KI, et al. Third-degree hindpaw burn injury induced apoptosis of lumbar spinal cord ventral horn motor neurons, sciatic nerve, muscle atrophy in rats. *Biomed Res Int*. 2015;2015:372819. doi:10.1155/2015/372819
12. Jiang X, Ma J, Wei Q, et al. Effect of Frankincense Extract on Nerve Recovery in the Rat Sciatic Nerve Damage Model. *Evidence-based complementary, alternative medicine : eCAM*. 2016;2016:3617216. doi:10.1155/2016/3617216
13. El-Derieny EA, Moustafa KA, Soliman GM. The possible protective role of ginseng on the sciatic nerve neuropathy induced experimentally by acrylamide in adult male albino rat: a histological, morphometric study. 2014;37(2):350-59. doi:10.1097/01.Ehx.0000446580.88948.42
14. Abdel-Daim MM, Abuzead SMM, Halawa SM. Protective Role of Spirulina platensis against Acute Deltamethrin-Induced Toxicity in Rats. *PLOS ONE*. 2013;8(9):e72991. doi:10.1371/journal.pone.0072991
15. Liu GM, Xu K, Li J, Luo YG. Curcumin upregulates S100 expression, improves regeneration of the sciatic nerve following its complete amputation in mice. *Neural Regen Res*. Aug 2016;11(8):1304-11. doi:10.4103/1673-5374.189196
16. Hayat MA. *Basic Techniques for Transmission Electron Microscopy*. Academic Press; 1986.
17. Schindelin J, Arganda-Carreras I, Frise E, et al. Fiji: an open-source platform for biological-image analysis. *Nature methods*. 2012;9(7):676-82.
18. Renno WM, Benov L, Khan KM. Possible role of antioxidative capacity of (-)-epigallocatechin-3-gallate treatment in morphological, neurobehavioral recovery after sciatic nerve crush injury. *J Neurosurg Spine*. Nov 2017;27(5):593-613. doi:10.3171/2016.10.Spine16218
19. Gundersen, H. J. G., Bendtsen, T. F., Korbo, L., Marcussen, N., Møller, A., Nielsen, K., Nyengaard, J. R., Pakkenberg, B., Sørensen, F. B., Vesterby, A., & West, M. J. (1988). Some new, simple and efficient stereological methods and their use in pathological research and diagnosis. *Journal of Microscopy*, 143(1), 3–45.
20. Calore EE, Cavaliere MJ, Puga FR, et al. Histologic Peripheral Nerve Changes in Rats Induced by Deltamethrin. *Ecotoxicology, Environmental Safety*. 2000/09/01/ 2000;47(1):82-6. doi:https://doi.org/10.1006/eesa.2000.1925
21. Kamel AMF. Histologic study on the protective effect of α-lipoic acid in sciatic nerve neurotoxicity induced by cypermethrin in albino rats. *Egyptian Journal of Histology*. 2011;34(2):218-30. doi:10.1097/01.Ehx.0000396638.08719.34
22. Ding R, Cao Z, Wang Y, et al. The implication of p66shc in oxidative stress induced by deltamethrin. *Chemico-Biological Interactions*. 2017/12/25/ 2017;278:162-9. doi:https://doi.org/10.1016/j.cbi.2017.10.005
23. Joy RM. Pyrethrins, pyrethroid insecticides: In: Joy RM, Ecobichon D, eds. *Pesticides, neurological diseases*. CRC Press. 1994:292-312.
24. Hansen MRH, Jørs E, Lander F, et al. Neurological Deficits After Long-term Pyrethroid Exposure. *Environmental Health Insights*. 2017/01/01 2017;11:1178630217700628. doi:10.1177/1178630217700628
25. Liao B, Newmark H, Zhou R. Neuroprotective Effects of Ginseng Total Saponin, Ginsenosides Rb1, Rg1 on Spinal Cord Neurons in Vitro. *Experimental Neurology*. 2002/02/01/ 2002;173(2):224-34. doi:https://doi.org/10.1006/exnr.2001.7841
26. Chang-Bum L, Min-Seok O. The Study on Regenerative Effects of Ginseng on Injured Axonal, Non-Neuronal cell. *The Journal of Korean Medicine*. 12 2008;29(5):14-28.
27. Frostick SP, Yin Q, Kemp GJ. Schwann cells, neurotrophic factors, peripheral nerve regeneration. *Microsurgery*. 1998;18(7):397-405. doi:10.1002/(sici)1098-2752(1998)18:7<397::aid-micr2>3.0.co;2-f

28. Calabrese EJ. Hormesis, ginseng: Ginseng mixtures, individual constituents commonly display hormesis dose responses, especially for neuroprotective effects. *Molecules*. 2020;25(11):2719. Published 2020 Jun 11. doi:10.3390/molecules25112719
29. Lu MC, Lai TY, Hwang JM, et al. Proliferation-and migration-enhancing effects of ginseng, ginsenoside Rg1 through IGF-I-and F.G.F-2-signaling pathways on RSC96 Schwann cells. *Cell Biochemistry,*
Function: Cellular biochemistry, its modulation by active agents or disease. 2009;27(4):186-92. doi:10.1002/cbf.1554
30. Wang W, Wang W, Chen H. Study progression in neuroprotective effects of ginsenoside Rg1. *J Bethune Med Coll*. 2005;10:291-3.
31. Chang C-J. The effect of pulse-released nerve growth factor from genipin-crosslinked gelatin in Schwann cell–seeded polycaprolactone conduits on large-gap peripheral nerve regeneration. *Tissue Engineering Part A*. 2009;15(3):547-57.
32. Wei C, Jia J, Wang F. Effects of ginsenosides Rg1, Rb1 on metabolism pathway of amyloid protein. *Chin J Inf Tradit Chin Med*. 2008;9:28-30.
33. Zhou P, Dong L, Yang Z, Fang Z. A study of the effects of ginsenoside Rg1 on regeneration of rat sciatic nerves. *Inn Mong Med J*. 2011;43:413-5.
34. Huo D-S, Zhang M, Cai Z-P, Dong C-X, Wang H, Yang Z-J. The role of nerve growth factor in ginsenoside Rg1-induced regeneration of injured rat sciatic nerve. *Journal of Toxicology, Environmental Health, Part A*. 2015;78(21-22):1328-37.

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