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Dietary supplementation with *Withania somnifera* root powder promotes recovery after peripheral nerve injury in mice

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Abstract: Commonly known as Indian ginseng or Ashwagandha, *Withania somnifera* (L.) Dunal has long been used as a medicinal herb that exhibits neuroprotective effects. Here, we investigate the potential impact of supplementing crude root powder of *W. somnifera* on restoring functions using a murine model. This model exhibits muscle function loss when subjected to a lesion to the sciatic nerve. A dose of 25 mg/kg of body weight was offered orally to the treatment group starting from the day of the nerve lesion to the end of the study. To evaluate the restoration of both muscle and sensory functions, the functional recovery was assessed through measuring the walking pattern (SFI), muscle force, and response to the thermal stimulus. Behavioural assessments were confirmed by evaluating the impact of treatment on oxidative stress, other systemic indicators, haematological, and serological markers. For all observations, a value of $p < 0.05$ was considered statistically significant. It was noted that the motor and sensory functions of the treatment group were markedly improved. We conclude that supplementing *W. somnifera* (roots) speeds up functional recovery following a peripheral nerve injury. For traumatic nerve injuries, it may be a therapeutic agent; however, further investigations are warranted.

Keywords: Motor functions; Nerve regeneration; Oxidative stress; Peripheral nerve injury; Sensory functions; *Withania somnifera* (L.) dunal

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INTRODUCTION

Phytochemicals, the naturally occurring bioactive compounds, are obtained from plants. They offer anti-inflammatory, anti-microbial, anti-diabetic, and several other beneficial properties both in health and disease conditions (Rodríguez-Negrete *et al*., 2024). Thus, they can prove a better alternative to synthetic drugs because of the lowest risk of side effects. Numerous studies report that various medicinal plants in crude or extract form offer neuroprotective effects in rodent models of traumatic injury (Hussain *et al*., 2019, 2018b, 2018a; Imran *et al*., 2019; Rasul *et al*., 2019).

Peripheral nerve injuries (PNIs) are the most common life-threatening conditions. PNIs are most frequently caused by gunshot wounds, car crashes, penetrating injuries, physical trauma, and falls. Despite the capability of regeneration following an injury, the functional reclamation of the affected organs is dead slow in ordinary conditions, and as a result, the muscle may get atrophied (Hussain *et al*., 2020; Lopes *et al*., 2022). The retarded process of regeneration and atrophied muscles appear to be a significant obstruction in the functional regain (Jabeen *et al*., 2023). This problem can be resolved by accelerating the process of regeneration before the muscular atrophy occurs. So, the need of the hour is to design effective therapies against such issues. Allopathic remedies and surgical methods have shown promising outcomes, but they come with a long list of negative consequences. Finding such compounds, mostly plant-derived ones, that can close this gap and speed up the healing process is therefore imperative.

Ashwagandha *(W. somnifera)* belongs to the family Solanaceae. The medicinal aspect of Ashwagandha against nervous exhaustion, memory loss, neuropathic pain, and insomnia was empirically recorded in Ayurveda by the ancient physicians (Mikulska *et al*., 2023; Nasir *et al*., 2024). The extracts of *W. somnifera* execute vast neuroprotective effects such as anti Alzheimer's disease, anti-convulsant, anti-inflammatory, anti-anxiety, anti-stress, and anti-oxidative (Khare and Vikram Naharwar, 2020; Sprengel *et al*., 2025). Furthermore, the root extract has also been found to induce neuroprotection and increase muscle mass and strength (Coope *et al*., 2025; Sajid *et al*., 2021). The root extracts are rich in phytochemicals and active constituents with neuroprotective properties, such as acylsteryl-glucoside, withanolide steroidal lactones, withanolide glycosides, and many beneficial alkaloids (Lerose *et al*., 2024; Ozeer *et al*., 2024). Data are scarce regarding the ability of *W. somnifera* to promote nerve regeneration and functional recovery, and based on the available data, we surmise that the functional regain process, after nerve injury, can be escalated by *W. somnifera.* Therefore, using a mouse model of peripheral nerve damage, we investigated the possible advantages of *W. somnifera* crude root powder in terms of hastening the recovery of nerve and muscle functioning after an injury.

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MATERIALS AND METHODS

Animals

The housing and handling of mice were performed at the animal housing facility of the Department of Physiology, Government College University, Faisalabad, Punjab, Pakistan. The study design used in this study was a non-randomised controlled study. The BALB/c male mice (n=14), weighing approximately 32-34g, with 6-7 weeks as their average age, were acclimatised for 7 days before experimentation, and they were kept at a temperature of about 22+3℃ and a 12-hour light/dark cycle. Regularly, mice were offered *ad libitum* water and a rodent chow diet. All behavioral parameters were accomplished under the significant rules and regulations of the Declaration of Helsinki and Stockholm Convention. All animal handling and experimental procedures were approved by the Institutional Animal Ethics Committee of the Government College University Faisalabad and were carried out in accordance with relevant national and international guidelines for the care and use of laboratory animals (e.g., NIH guidelines or CPCSEA, if applicable). All behavioral assessments and experimental interventions were performed with due consideration to animal welfare.

Induction of compression injury to sciatic nerve

The sciatic nerve of the right leg was given a compression injury according to "Ali Imran's" earlier description (Imran *et al*., 2019). Briefly, Xylazine at 5 mg/kg and ketamine at 70 mg/kg doses were injected intraperitoneally into the mice to anesthetise them. The site of incision was shaved neatly, and the skin was incised along the proximal half of the speck between the knee joint and the trochanter major for a distance of 2 cm. The right hind limb's sciatic nerve was crushed, while the left one remained intact. Using a pair of forceps, constant pressure was applied for 15 seconds to cause a lesion to the target nerve. We visually confirmed that the target nerve was properly lesioned with intact epineurium. Visual observation was used to confirm that the nerve was properly compressed and that the epineurium was still intact. Mice were put on the hot pad after the incisions were closed with 4-0 stitches. Mice were split into two groups following the induction of injury: the treatment group (n = 7) and the control group (n = 7).

Plant material preparation and supplementation

The Department of Botany of our university (Government College University, Faisalabad) verified the identification of the plant material, *W. somnifera*, which was bought from the market of Faisalabad city (Herbarium Number 245-bot-18). The plant material preparation for supplementation was done as already described by "Azhar Rasul" (Rasul *et al*., 2019). After being washed and allowed to dry in the shade, the roots were powdered with a mesh size of 60. The powder was passed through a mesh to remove fibres and coarse particles. A minimum effective dose of 25mg/kg body weight was selected from the pilot study on effective dose selection by using 25mg, 50mg, and 100mg (data not shown). In the mouse chow diet, a measured quantity of powdered crude roots was added at a level of 25 mg/kg body weight. An average daily food intake of 6g was ensured to contain the necessary amount of root material. The diet containing doses was given to the treatment group starting from the first day of injury induction and continued for the entire duration of the study. Daily measurements were made of the average body weight and food consumption.

Behavioral tests

Muscle gripping force

A grid or horizontal metal bar is used to measure a mouse's muscular strength in vivo. (Bioseb, Chaville, France) as previously reported by (Aziz *et al*., 2019; Hussain *et al*., 2013; Imran *et al*., 2019). Both paws' (contralateral and ipsilateral) muscle grip strength force (as a % of initial force) was assessed, and an average of three readings was measured for each of the mice. The motor functional regain was ensured by comparing the readings between the normal group and the experimental group.

Movement pattern (sciatic functional index)

The movement pattern of animals is evaluated by measuring SFI, which was also used to assess motor function recovery, as reported earlier (Aziz *et al*., 2019; Imran *et al*., 2019; Rasul *et al*., 2019). The hind paws of mice were dyed with an ink, preferably blue ink, and they were permitted to walk on the wooden track covered in white paper. The formula below was used to calculate the SFI for the observable prints per run (Bain *et al*., 1989):

$$SFI = \left(-38.3 \times -\frac{EPL - NPL}{NPL}\right) + \left(109.5 \times \frac{ETS - NTS}{NTS}\right) + \left(13.3 \times \frac{EIT - NIT}{NIT}\right) - 8.8$$

In the equation given above, IT is the distance between intermediate toes, TS is the total spread of the paw, i.e., distance from the 1st to the 5th toe, and PL stands for the print length, i.e., distance from the heel to the peak of the 3rd toe. Whereas NIT, NTS, and NPL represent the SFI measurement for the contralateral (normal) paw, and EIT, ETS, and EPL are the measurements for the ipsilateral (experimental) paw.

Hot plate test

The regain of sensory functions was assessed by performing a hotplate test (SCILOGEX MS7-H550-S LED digital 7x7 Hotplate stirrer) as described earlier by "Nimra Aziz and Ali Imran" (Aziz *et al*., 2019; Imran *et al*., 2019). Briefly, before the start of the experiment, the mice were all acclimated to the non-working apparatus for a minute. The ipsilateral paw of each mouse was exposed to the heated surface of a hotplate with a temperature setting of 56+2°C The very first response of either licking or jerking was noticed and recorded as the hotplate latency (HPL). Three readings in all, separated by two minutes, were recorded. If the mouse did not react to the paw withdrawal reaction within 30 seconds, the heat stimuli were stopped to avoid tissue damage.

Biochemical tests

Total oxidative status (TOS)

Oxidative stress is thought to be one of the numerous effects of neurological damage following peripheral nerve injury. By monitoring TOS, one may assess the oxidative status of the entire body. The detailed procedure has been explained earlier by (Aziz *et al*., 2019; Imran *et al*., 2019).

Total antioxidant capacity (TAC)

Antioxidants are important because they guard against the harmful effects of free-moving radicals. The total antioxidant ability of a biological system can be measured by performing TAC. A detailed description of TAC performance has been described earlier by "Nimra Aziz and Ali Imran" (Aziz *et al*., 2019; Imran *et al*., 2019).

Muscle weight

Weighing the muscles allowed us to evaluate the extent of muscular atrophy. The mass was measured using the Tibialis Anterior (TA) and Gastrocnemius muscles in both the normal chow and *W. somnifera* chow groups. The weights of the ipsilateral legs of the treated and untreated mice were compared in order to ascertain whether there was a significant difference in muscle mass between the two groups.

Random blood glucose

Measurement of random blood glucose was performed by using a glucometer (Accu-check) and a glucose strip. A sterilised lancet was used to prick the coccygeal vertebra to take a drop of blood. The protocol was adopted by Brăslaşu *et al* (Brăslaşu *et al*., 2007).

Statistical analysis

GraphPad Prism version 10.4.2 was used for statistical analysis. Group means were statistically compared through an independent sample t-test. A value of $p<0.05$ with a 95% Confidence Interval was considered statistically significant.

RESULTS

Impacts of W. somnifera on body mass and food intake

During the whole experiment (before and after nerve lesion), we recorded the food intake and body mass. There were no significant differences in the *W. somnifera* chow-treated group and normal chow groups before and after nerve injury (Fig. 1A). It depicts that *W. somnifera* did not alter body mass. Moreover, the food intake in both groups was almost equivalent in the pre- and post-surgery period of the entire experiment (Fig. 1B). The presence of *W. somnifera* in the mice's diet did not modify the food intake pattern and animal liking for food. It ensures that the results (positive or negative) are entirely due to *W. somnifera* addition in the mice's diet.

W. somnifera accelerates motor function retrieval

Muscle mass, grip strength, and the SFI (Sciatic Functional Index) were used to gauge the recovery of motor skills. The muscle grip strength of the treatment group was significantly improved (Fig. 2A). The recovery trend observed in the SFI assessment was also enhanced in the *W. somnifera* chow group (Fig. 2B). Another authentic parameter regarding the evaluation of functional recovery is measuring muscle mass. The muscle mass of the Gastrocnemius was significantly enhanced, nearly equivalent to the contralateral hind limb in the *W. somnifera* chow group (Fig. 2C - lower panel). The achieved results may lend credibility to the notion that the crude form of *W. somnifera* can accelerate functional regain. Additionally, the improved mass was also noticed in the TA muscles of the *W. somnifera* chow group, but the results were not statistically significant (Fig. 2C - upper panel).

W. somnifera accelerates sensory function retrieval

Due to its mixed composition, damage to the sciatic nerve impairs both motor and sensory functions. In our experiment, the thermal response was assessed by the hotplate test. Although the results were not statistically significant, a reduction in the latency for withdrawal in the hind paw (ipsilateral) was observed in the *W. somnifera* chow group (Fig. 3).

Impact of W. somnifera on the systemic indices

The muscle grip strength, SFI, and other approaches strengthened our proposed hypothesis that *W. somnifera* could somehow improve the rate of functional recovery. To gain insights regarding the possible mechanism, we investigated the impact of *W. somnifera* on haematological markers, oxidative stress, and glucose metabolism.

First, we performed the haematological analysis and assessed RBCs, WBCs, platelet count, and haemoglobin level. These findings revealed that the haemoglobin level was elevated significantly in response to *W. somnifera* supplementation. In contrast, the blood cell count was non-significant statistically (Fig. 4A). The random blood glucose levels in both the *W. somnifera* chow and normal chow mice groups were checked to reveal the effects of *W. somnifera* on glucose metabolism. The data regarding glucose levels were statistically significant, ensuring better glycemic control in the *W. somnifera* treatment group (Fig. 4B). Additionally, oxidative stress during neuronal injury may lead to further neural damage.

TOS and TAC are normally used to evaluate the overall oxidative stress status of a biological system of a body. Interestingly, we found that the results of TAC (Fig. 4C upper panel) and TOS (Fig. 4C lower panel) were highly significant in the *W. somnifera* chow group, indorsing the antioxidant capability of *W. somnifera.*

DISCUSSION

Peripheral nerve injuries (PNIs) are among the most challenging medical conditions to treat and they affect a

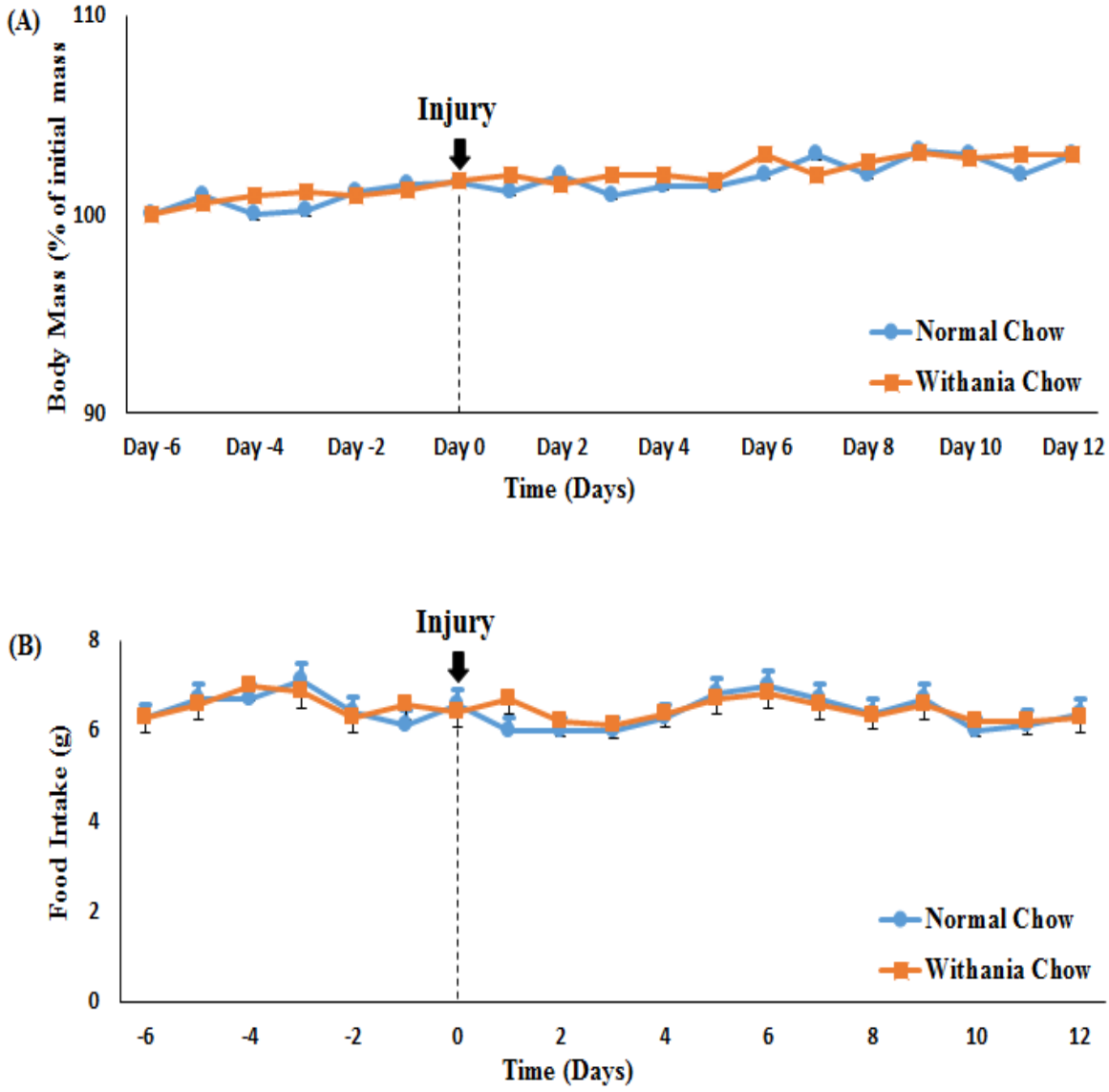

Fig. 1: The figure depicts the effect of *W. somnifera* on body weight and food consumption.
(A) Body weight progression over time in mice fed with *W. somnifera* chow (n=7, orange squares) or on normal chow (n=7, blue circles). Mice were nourished on *W. somnifera* containing chow from the day of nerve crush (day 0, dotted line) till the end of the experiment. The independent sample t-test (with a p-value of $p<0.005$) showed a non-significant effect of *W. somnifera* on body mass ($p=0.636$) and a non-significant interface b/w factors ($F=0.002$, $p=0.962$). (B) Time course of food intake of mice. Non-significant difference was shown by independent sample t-test in diet consumption b/w control and the treatment group ($p=0.071$) and noticeably a non-significant interaction b/w factors ($F=1.95$, $p=0.187$).

large number of populations throughout the world. As a consequence of such conditions, both motor and sensory functions are lost, which may lead to lifelong dependence and social stigmatisation. Although peripheral nerves have the inherent ability to regenerate and reinnervate target muscles, the process may take weeks to years, depending on the severity of the injury. This delayed regeneration often leads to distal muscle atrophy, further complicating recovery and exacerbating the situation. The accurate and complete functional regain depends on various factors, including the nerve regeneration rate, which is unfortunately very slow under ordinary circumstances, and is thought to be a leading player.

Accelerating nerve regeneration is essential to facilitating functional recovery and halting the progression of muscle atrophy. A large number of therapeutic strategies have been designed and practiced to address this issue. Despite encouraging outcomes, these approaches have shown many side effects that have resulted in their limited usage. To date, no available interventions have proven fully effective in addressing this condition. In this scenario, the need for new approaches and materials for the treatment appears even stronger.

Plant-based remedies have been used since ancient times and continue to offer viable options in modern medicine.

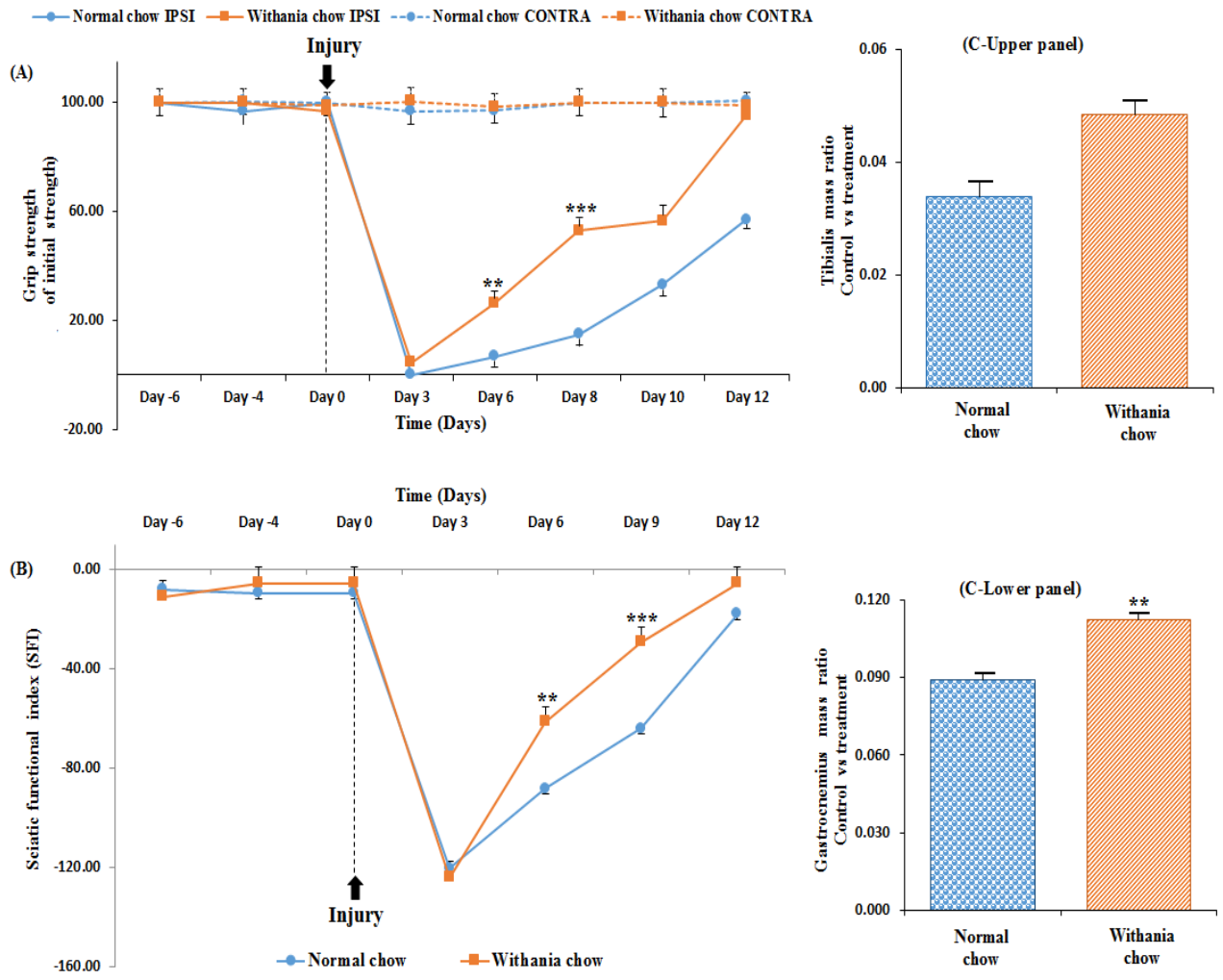

Fig. 2: *W. somnifera* accelerates the motor function regain after an injury to the sciatic nerve.
(A) A time course of muscle grip strength in mice. The measurements were taken from the hind limbs ipsilateral (solid lines) and contralateral (dotted lines) to the nerve lesion. The grip strength was recorded in the percentage of initial muscle force. The independent sample t-test showed a significant effect of diet. A significant difference between *W. somnifera* and the normal chow group was found on day 6 ($F=1.300$, $^{**}p<0.01$) and day 9 ($F=9.127$, $^{***}p<0.0001$) after the nerve lesion. (B) The progression of sciatic functional index over time in mice receiving *W. somnifera* chow (n=7, orange squares) or normal chow (n=7, blue circles). The mice were given *W. somnifera* chow from the day of nerve crush (day 0, dotted line) till the end of the experiment. A significant difference was detected between *W. somnifera* and the normal chow group of mice on day 6 ($F=4.592$, $^{**}p<0.01$) and day 9 ($F=0.614$, $^{***}p<0.0001$) after the nerve lesion. (C) Tibialis (upper panel) and gastrocnemius (lower panel) muscle mass as described above in A. The quantities are taken as a ratio b/w the hind limb contralateral and ipsilateral to the nerve lesion. The independent samples t-test revealed a significant dietary effect on the gastrocnemius muscle ($^{**}p<0.01$).

Plants and their extracts promote earlier functional regain. Although such studies are very preliminary, they are imbued with the ultimate hope of shortening the nerve regeneration period (Aziz *et al*., 2019; Hussain *et al*., 2013; Imran *et al*., 2019). The current study is the continuation of our efforts to discover the most potent bioactive molecules of plant origin. Here, we evaluate the widely used crucial medicinal plant of the Indian Subcontinent, *W. somnifera,* otherwise referred to as Indian ginseng (Kuboyama *et al*., 2014).

Numerous neuroprotective effects of *W. somnifera*, including anti-Alzheimer, anti-convulsant, anti-inflammatory, anti-anxiety, anti-stress, and anti-oxidative properties, have been thoroughly investigated; however, no information about its effect on peripheral nerve injury recovery has been published. Using the sciatic nerve injury model we have developed for rodents (mice), we explored the possible role of crude root powder of *W. somnifera* on the rate of function recovery after a traumatic injury to the sciatic nerve. Our findings show an expeditious retrieval of motor functions in the *W. somnifera*-supplementeded mice group. Significant improvements in grip strength and SFI were observed as early as day 6 post-injury ($p < 0.01$).. Muscular atrophy is a leading cause of disability after PNI, and it results in reduced muscle mass (Hoke and Brushart,

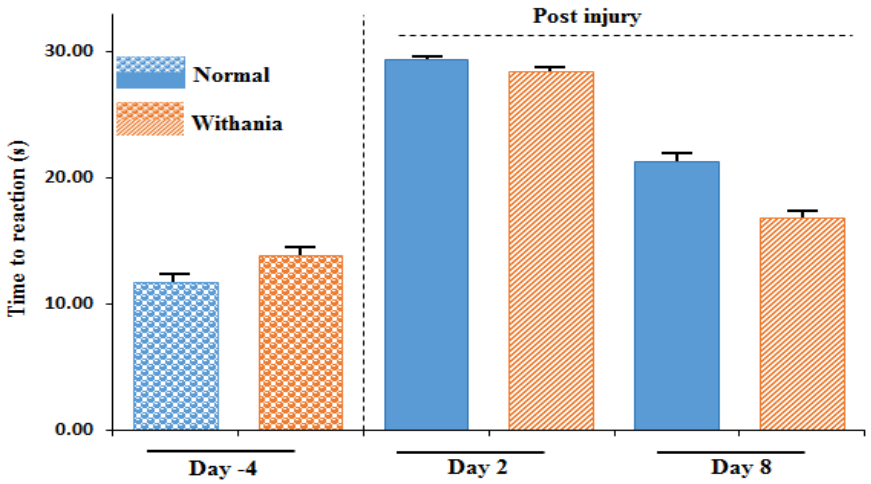

Fig. 3: *W. somnifera* indicated a trend of improved thermal response.
The latency of withdrawal in response to thermal stimulus in mice fed on *W. somnifera* chow (n=7, orange bars) or normal chow (n=7, blue bars). Pre- and post-lesion measurements were recorded. The independent sample t-test showed a non-significant outcome of treatment on a thermal response (F=8.295, p=0.313).

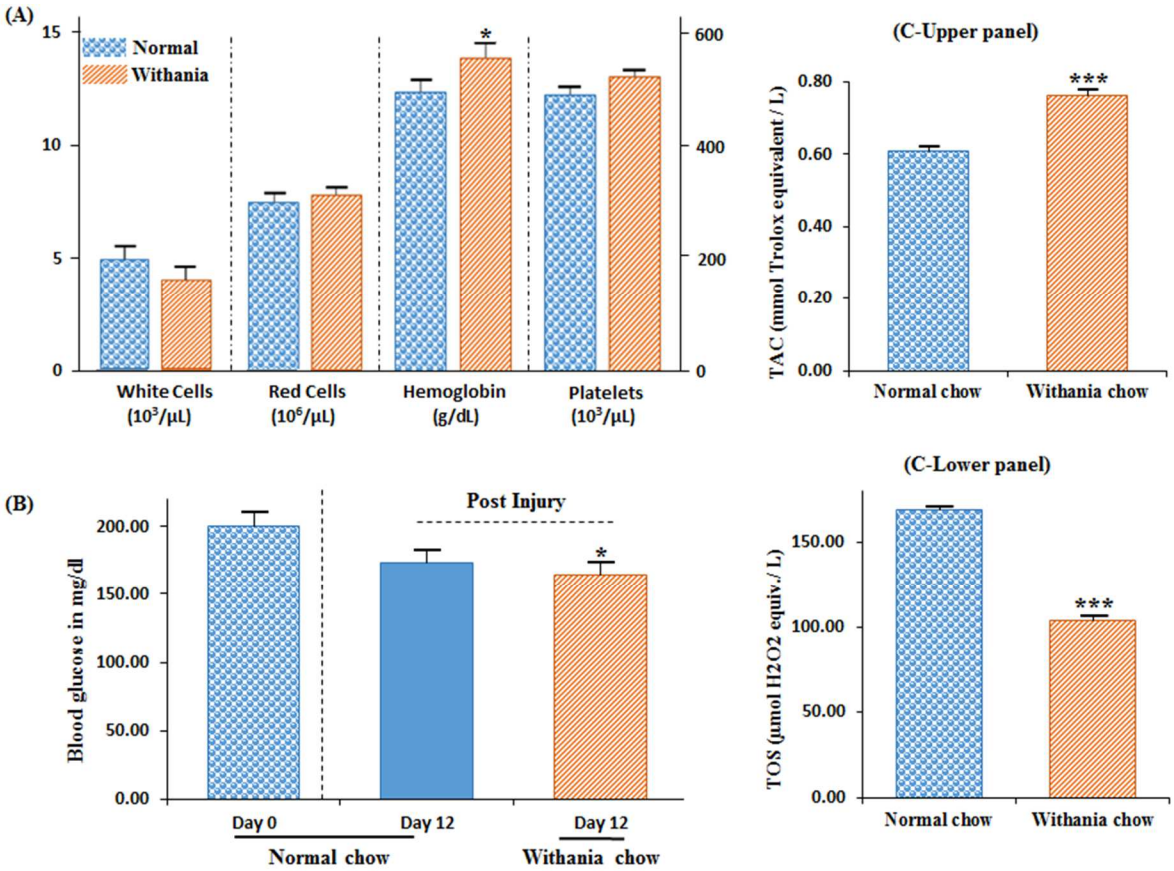

Fig. 4: Impact of *W. somnifera* on the systemic indexes. (A) Hemoglobin contents and blood cells count in mice fed on *W. somnifera* chow (n=7, orange bar) or on normal chow (n=7, blue bar). The measurements were taken at the end of the experiment subsequent to function regain. The independent sample t-test showed a significant effect on each parameter (*p<0.05). (B) Glucose in the animals as described in the panel A and at the time of lesion (n=7, blue hatched bar, day 0); and subsequent 12 days of function regain following peripheral nerve injury in mice fed on *W. somnifera* chow (n=7, orange bar); or normal chow (n=7, blue solid bar). The independent sample t-test showed a statically significant outcome (*p<0.05). (C) Total Oxidant Status (lower panel) and Total Antioxidant Capacity (upper panel) of mice as described in A. The independent sample t-test showed a significant effect on oxidant status (***p<0.0001).

2009; Richner *et al*., 2014; Tuffaha *et al*., 2016). An upsurge in muscle mass was noticed in the treatment group, suggesting protective effects. The muscle mass of both the Gastrocnemius ($p<0.01$) and TA muscles was improved in the treated group, nearly equivalent to the muscle mass of the hind limb contralateral to the lesion. This suggests that *W. somnifera* roots in crude form have the capability to retrieve nerve functionality and also help in preventing the exacerbation of muscular atrophy. Oxidative stress is a leading hallmark of neuronal damage that results in mitochondrial dysfunction, apoptosis, neuroinflammation, and demyelination. Previous studies indicate that *W. somnifera* roots possess the capability to alleviate neuroinflammation, regulate apoptosis, and modulate mitochondrial functions by reducing the reactive oxygen species (ROS) (RajaSankar *et al*., 2009)(Dar *et al*., 2015). Our findings are also consistent with these studies because highly significant ($p<0.0001$) anti-oxidative properties of *W. somnifera* were observed. There are many active constituents reported in *W. somnifera* roots - for instance, sitoindosides VII and VIII (acylsteryl-glucosides), sitoindosides IX and X (glycowithanolides), withanine and withananine (alkaloids), and ashwagandhanolide (Bilal Ahmad Mir, Jabeena Khazir, Nisar A. Mir, 2012). The entire positive sequel observed in our study might be due to the contribution of any of the above active constituents, which require further investigations to identify and characterise these constituents. However, this observation requires further and detailed investigation at the molecular level. That will lead to the identification of novel drug candidates.

The regain of sensory functions of the mixed nerve type sciatic nerve is also examined to assess the pattern of functional recovery. We found an observable change in the withdrawal potential of the ipsilateral paw (hind) in the *W. somnifera* chow mice group. These findings further support the neuroprotective potential of *W. somnifera* and underscore the need for additional research at the molecular level. Recently, it has been reported that increased hemoglobin level is one of the factors involved in functional regain (Aziz *et al*., 2019). In our study, we also found that *W. somnifera* significantly elevates the haemoglobin level in the treated group ($p<0.05$) when compared to the animals of the untreated group. Moreover, while discussing peripheral nerve injury, altered glucose metabolism has also been a moot issue. The primary cause of the elevated glucose levels in the surrounding environment of the injury site is the start of numerous harmful metabolic cascades, which may ultimately impede the process of healing and regeneration. "Li" *et al*. (2004) reported the anti-diabetic property of *W. somnifera,* and our findings also support this report. The data regarding the glucose-reducing capability of *W. somnifera* was statistically significant ($p<0.05$), ensuring the anti-diabetic effects of *W. somnifera* roots. We speculate that this glucose-lowering effect indirectly increases the metabolic rate to combat the injury, as observed by Hussain *et al,* 2013. A lot of studies witness a dose-dependent effect of this plant extract, though no such difference was appreciated in our research. Such a robust result at a low dose of 25 mg/kg can be attributed solely to the bioactive compounds present in the root extract, without having off-target or toxic effects due to higher doses. Identification and characterisation of bioactive molecules of *W. somnifera* that are accountable for these effects are highly recommended for their potential clinical use. As the current study lacks molecular endpoint validation (e.g., gene expression, axonal markers, histology), further work examining the effects of additional plant parts on promoting sciatic nerve regeneration will be highly thought-provoking. Investigating the anatomy of muscle and nerve fibres, as well as the molecular mechanisms behind this entire narrative, will also be of considerable interest.

CONCLUSION

In summary, the results of this investigation indicate that the use of powdered crude *W. somnifera* root may accelerate the recovery of neuronal function after a nerve compression injury. According to our findings, *W. somnifera* may be a new restorative option for peripheral nerve regeneration in cases of traumatic nerve damage. Even still, these findings are quite preliminary and call for more thorough research to identify the powerful ingredients and processes that support the healing process.

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Author's contributions
FS and GH conceived and designed the experiment. FS performed the experiment, and MZ and AI contributed to analysing and the interpretation of data. FS and GH contributed to the drafting of the manuscript.

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Data availability statement
All data generated or analysed during this study are included in this published article.

Ethical approval
The present study design and rodent model (mouse) usage for this study were formally reviewed, and thereafter approval was granted for this study by the ECR (Ethics Review Committee) of this university (Ref. No. GCUF/ERC/307-A).

Conflict of interest
All authors affirm that there exists no conflict of interest among them.

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