

## Original Research Article

# ***Ferula asafoetida* Linn. is effective for early functional recovery following mechanically induced insult to the sciatic nerve of a mouse model**

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### **Abstract**

**Purpose:** To evaluate the effect of *Ferula asafoetida* (oleo gum resin powder) on sensory and motor functions retrieval on an induced sciatic nerve injury in a mouse model.

**Methods:** A mechanical crush was inserted in the sciatic nerve of all the experimental mice after acclimatization. The mice were allocated to four groups; one normal chow group (control, n = 7) and three *Ferula asafoetida* chow groups (each n = 7) of different doses (50, 100 and 200 mg/kg). Muscle grip strength, muscle mass, and sciatic functional index were measured to evaluate the motor function regain, while sensory function regain was assessed by hot plate test. Oxidative stress and glycemic levels were measured by biochemical assays.

**Results:** The findings of this study indicate that *Ferula asafoetida* 200 mg/kg has a highly significant ( $p \leq 0.001$ ) ameliorating effect in terms of improved grip strength ( $77.7 \pm 5.4$  % for 200 mg/kg vs.  $46 \pm 5.1$  % for control), reversal of SFI towards normal ( $-34 \pm 8.1$  for 200 mg/kg group vs.  $-61 \pm 6.1$  for control), decrease in paw withdrawal latency ( $7.10 \pm 0.06$  s for 200 mg/kg group vs.  $15 \pm 0.5$  s for control) on day 12 post-injury, as well as restoration of skeletal muscle mass towards normal. Interestingly, *F. asafoetida* chow 50 mg/kg and 100 mg/kg groups also impacted significant ( $p < 0.01$ ) improvement in the ameliorative effect. However, the differences among all treatment groups in ameliorating recovery were not significant ( $p > 0.05$ ). Moreover, comparatively improved ( $p < 0.0001$ ) total antioxidant capacity along with reduced total oxidant status ( $p = 0.01$ ) in the *Ferula asafoetida* chow (200 mg/kg) group, indicate the antioxidative effect of this plant. Furthermore, the treated mice (200 mg/kg) also expressed an improved glycemic level ( $p = 0.0005$ ).

**Conclusion:** *Ferula asafoetida* supplementation helps to accelerate both sensory and motor function retrieval following sciatic nerve injury. This improvement is thought to be correlated with the antioxidant capacity of the plant. However, further investigations are required to identify the therapeutic principles responsible for the observed actions.

**Keywords:** Sciatic nerve injury, *Ferula asafoetida*, Function recovery, Oxidative stress, Biochemical analysis

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## INTRODUCTION

Peripheral nerve injury (PNI) stands among the most prevalent and complex medical situations that is characterized by a partial or complete functional disability. Effective therapy for a thoroughly perfect restoration of physical activity has been a challenge until now. PNI may be a consequence of road accidents, physical or mechanical traumas, gunshots, bone fractures compressing nearby nerve, etc. Although there is an ability of self-repair in the peripheral nervous system (PNS), this process is terribly sluggish [1,2]. In addition to other miscellaneous factors, a very slow regeneration, accompanied with muscular atrophy is found to be the main obstacle to achieving functional recovery [3].

Although a variety of medicinal and surgical approaches are in practice to treat PNI, none of them can lead to a complete restoration of nerve function. Therefore, a perfect recovery of physical function always appears an unbeatable challenge. Plants are considered as a constant and inexhaustible source for the discovery of drug candidates since the beginning. Nowadays, considerable emphasis has been made on figuring out therapeutically effective strategies based on novel bioactive compounds from plants. Even in the modern age, natural compound-based approach is preferred to allopathic drugs in many parts of the world because of their invincible advantages, such as abundant availability, easy accessibility, and minor to no side-effects [3–6]. Therefore, such plant-sourced compounds which are effective enough in speeding up function retrieval, would prove a revolution in the field of medicine [7]. Thus, these natural compounds present an auspicious alternative therapeutic approach.

*Ferula asafoetida* (*F. asafoetida*) from *Umbelliferae* family, is cultivated in most parts of the world, including the Middle East and Indian sub-continent. An oleo-gum-resin, commonly known as asafoetida, is obtained from the exudates of the roots of this plant [7]. Asafoetida has been used as a spice and a folk phytomedicine for centuries. *F. asafoetida* is effective against anxiety, convulsions, epilepsy, peripheral neuropathy, and mood disorders. It is also used as a nerve stimulator and sedative agent [8]. *F. asafoetida* can be a reliable candidate for PNI because of its reported neuroprotective effects. But its role in accelerating function retrieval following PNI has not been investigated. Therefore, this study was planned to unravel the possible effectiveness of *F. asafoetida* on the rate of functional restoration

in an already established rodent model of compression injury.

## EXPERIMENTAL

### Animals

Healthy male albino mice (10 - 12 weeks old, and 28 - 30 g weight) were procured from the animal facility in GC University, Faisalabad. They were housed in separate rodent cages at ambient room temperature ( $23 \pm 2$  °C), in a humidity-controlled environment, and a 12 hours light and dark cycle with *ad libitum* supply of rodent chow diet and drinking water.

The protocols for the use and care of animals in this study were based on the rules provided by the National Institute of Health (NIH) for the use and care of experimental animals [24]. The design of the study was sanctioned by the IRB (Institutional Review Board), GC University Faisalabad (ERB no. 3845).

### Collection and processing of plant material

*F. asafoetida* (oleo gum resin) was acquired from the market in Faisalabad, Pakistan. The Department of Botany was consulted for the identification of the plant. The plant material was ground and mixed in rodent chow feed at 50, 100 and 200 mg/kg of body weight [8,9]. The dosage was adjusted in such a way that the daily average consumed diet must contain the required dosage of the plant. This was calculated using Eq 1.

$$D = W (Dd/1000) \dots\dots\dots (1)$$

where D, W and Dd are daily dose, weight of rat, and dose per kg body weight, respectively.

### Introduction of nerve injury

The injury was introduced mechanically to the sciatic nerve following a standard published protocol [10]. The mice were briefly sedated with a ketamine (70 mg/kg) and xylazine (5 mg/kg) mixture by giving an intraperitoneal injection. The nerve was made visible and manually crushed with forceps for 15 sec at the mid-thigh region of the right hindlimb. The incisions were sealed with 3 - 4 sutures.

### Animal study design

After introducing the nerve injury, the mice were separated into four groups named as, normal chow (Control, n = 7), *F. asafoetida* chow 50 mg (n = 7), *F. asafoetida* chow 100 mg (n = 7), and

*F. asafoetida* chow 200 mg (n = 7). From the day of the nerve crush until the end of the study, the control group was given normal rodent feed, while *F. asafoetida* chow groups were offered the feed containing the calculated doses of *F. asafoetida* oleo gum resin. At the termination of the experiment, the mice of all groups were sacrificed using deep anesthesia as mentioned above. Blood was collected for biochemical analyses and skeletal muscles from both Ipsi and Contra hindlimbs were dissected to measure muscle mass ratio.

### Assessment of sensory function

Retrieval of sensory function was assessed by applying thermal stimulus (**Hot-plate test**) using a hotplate (SCILOGEX MS7-H550-S LED digital 7 x 7 Hotplate stirrers). The method was carried out according to the standard protocol described by Haas, 2010 [11]. The mouse was briefly allowed to stand on a hot surface set at  $56 \pm 1$  °C in such a manner that the ipsilateral paw would be on the hot surface. The time taken for the withdrawal response (jumping, tapping, or jerking of the paw) was noted. A total of 3 readings were recorded at an interval of 2 min between successive readings. If the mouse did not respond in 30 sec (cut-off time), the stimulus was terminated to prevent skin burning [6].

### Assessment of motor function

#### Sciatic functional index (SFI)

The motor function of all mice was evaluated by assessing SFI. The hind paws of the mouse were painted with non-toxic ink and placed on a wooden track (having a white plain sheet on its surface) to walk towards the darkened box. This enables us to get the paw prints of the mouse on a white sheet, which were analyzed by using the following equation to get SFI (Eq. 2):

$$\text{SFI} = (-38.3 \times (\text{EPL} - \text{NPL}) / \text{NPL}) + (109.5 \times (\text{ETS} - \text{NTS}) / \text{NTS}) + (13.3 \times (\text{EIT} - \text{NIT}) / \text{NIT}) - 8.8 \dots \dots \dots (2)$$

where print Length (PL) is the distance between the heel and tip of the 3<sup>rd</sup> toe; the intermediate toes spread (IT) is the distance between the 4<sup>th</sup> and 2<sup>nd</sup> toe, and toe spread (TS) is the gap-length between the 1<sup>st</sup> and 5<sup>th</sup> toe. The N indicates the normal paw measurements as NPL, NIT, and NTS, whereas E stands for the experimental paw measurements as EPL, ETS, and EIT [10].

### Muscle grip strength

Grip strength test was carried out according to the procedure elaborated by Hussain *et al*, 2013 [12]. The grip force (N) of both hind limb muscles (contralateral and ipsilateral to the injury site) was measured using a grip strength meter (Bioseb, Chaville, France). The mean of the triplicate readings was taken.

### Biochemical analysis

#### Total antioxidant capacity

Antioxidant capacity is the capability of a bio-system to scavenge the free radicals and associated mal-functionalities. TAC (Total Antioxidant Capacity) assay was performed according to the protocol described earlier [10] to measure the antioxidant capacity in serum samples of all animals.

#### Total oxidant status (TOS)

The level of oxidative stress is known to be correlative with the extent of Total Oxidant Status (TOS) within the living system. Using this test, the overall status of the TOS ( $\mu\text{mol H}_2\text{O}_2$  Equivalent/L) was estimated using the protocol described elsewhere [10].

#### Random blood glucose

The glycemic level was analyzed with the help of a glucometer (Accu-check). A blood drop was oozed out from the tail of the mouse and was analyzed by using the method used by Asmat *et al*, 2016 for glucose level [13].

### Statistical analysis

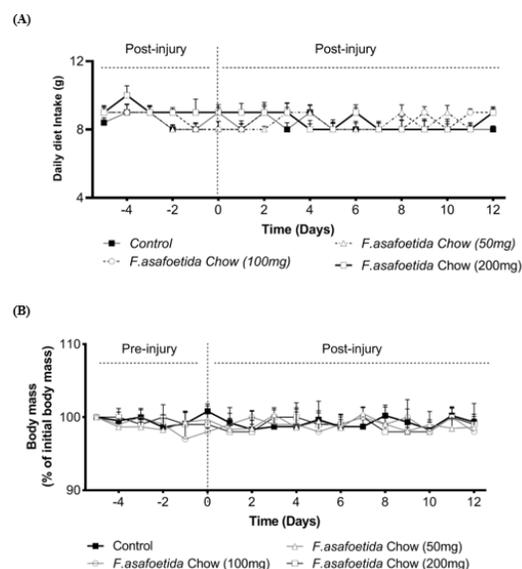
All results are presented as mean  $\pm$  SEM. Data were statistically analyzed using GraphPad Prism (version 8.4.2). ANOVA was used to compare the mean of all groups, followed by Tukey's multiple comparisons test. For statistical significance, a value of  $p < 0.05$  was assumed.

## RESULTS

### Impact of *F. asafoetida* on feed intake and body mass

The daily feed intake was measured throughout the experimental period. A statistically non-significant effect ( $p = 0.23$ ) of diet consumption patterns was discovered among all groups. Tukey's multiple comparisons test did not reveal any significant differences among any pair or groups on any day (Figure 1 A). It indicates that

the *F. asafoetida* addition in the animal feed did not alter the taste of the food, and clearly depicts that the obtained results were dependent on the presence of *F. asafoetida* in the feed. In addition, the daily bodyweight of every animal was recorded, and no statistically significant difference ( $p > 0.99$ ) was noted among all groups on any given day. This indicates that all selected doses of *F. asafoetida* were safe and did not cause any harmful changes in body metabolism (Figure 1 B).

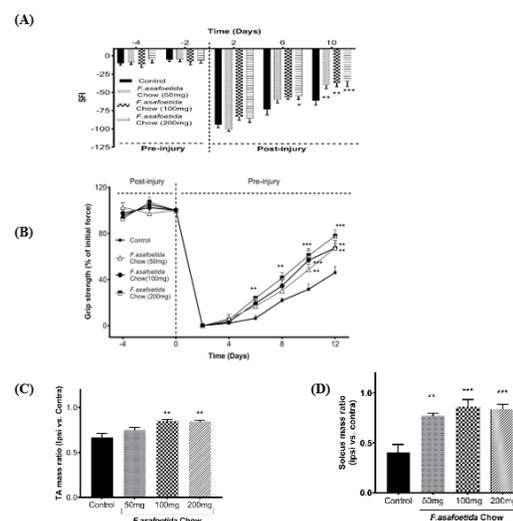


**Figure 1:** Effect of *F. asafoetida* on daily feed intake (A) and body mass (B). Results are mean  $\pm$  SEM; (A) Time course of feed intake in animals fed on normal chow (control  $n = 7$ ), *F. asafoetida* chow 50mg ( $n = 7$ ), 100 mg ( $n = 7$ ) and 200 mg ( $n = 7$ ). Two-way repeated measure ANOVA, along with Tukey's multiple comparison test indicated non-significant differences ( $p = 0.23$ ) among all the groups. (B) Time course of body mass of mice served with normal chow (control  $n = 7$ ), *F. asafoetida* chow 50mg ( $n = 7$ ), 100 mg ( $n = 7$ ) and 200 mg ( $n = 7$ ). Two-way repeated measure ANOVA, along with Tukey's multiple comparison test displayed non-significant differences ( $p > 0.99$ ) among all the groups

### *F. asafoetida* accelerates motor function recovery

The motor function recovery was evaluated using SFI, grip strength test (percentage of initial force in N), and muscle mass ratio. These parameters are helpful in evaluating the progression of function regained after sciatic nerve injury. Results were statistically evaluated by applying two-way repeated-measures ANOVA. Motor function was significantly improved in *F. asafoetida* chow groups, more than that observed in the control group ( $p = 0.007$ ). Tukey's multiple comparisons test revealed that

*F. asafoetida* chow group (200 mg/kg) was significantly more effective in improving SFI at day 6 ( $p = 0.02$ ), while other treatment groups were found to be non-significant ( $p = 0.08$ ). On day 10, all treatment groups showed significantly improved SFI ( $p = 0.007$ ) as compared to the control group, particularly the 200 mg/kg treated groups, which showed highly significant ( $p = 0.0004$ ) improvement in SFI (Figure 2 A).



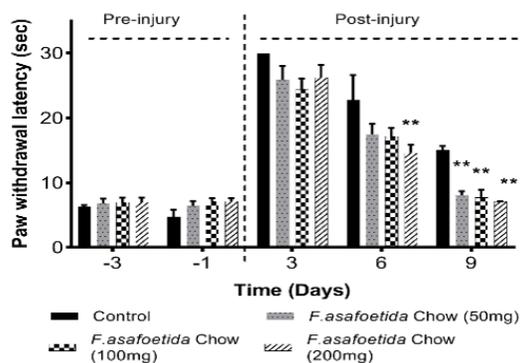
**Figure 2:** Effect of *F. asafoetida* on motor function recovery. Results are mean  $\pm$  SEM; (A) Time course of Sciatic Function Index for mice served with normal chow (control  $n = 7$ ), *F. asafoetida* chow 50 mg ( $n = 7$ ), 100 mg ( $n = 7$ ) and 200 mg ( $n = 7$ ). The two-way repeated measure ANOVA, along with Tukey's multiple comparison test showed that *F. asafoetida* chow 200 mg significantly improved SFI as compared to the control group on days 6 ( $p = 0.02$ ) and 10 ( $p = 0.0004$ ) post-injury. (B) Time course of muscle grip force for mice as in A. The Two-way repeated measure ANOVA, along with Tukey's multiple comparison test showed that *F. asafoetida* chow 200 mg significantly improved grip strength on days 6, 8, 10 and 12 ( $p < 0.0001$ ) post-injury. (C) TA muscle mass ratio and (D) Soleus muscle mass ratio of groups as in A. Ordinary one-way ANOVA along with Tukey's multiple comparisons tests showed that *F. asafoetida* chow 200 mg significantly increased the muscle mass ratio of TA ( $p = 0.002$ ) and soleus ( $p = 0.0003$ ) as compared to the control group

However, comparative differences among all treatment groups (50, 100 and 200 mg/kg) was found to be non-significant ( $p = 0.9$ ). The grip strength force was significantly augmented in the *F. asafoetida* chow group (200 mg/kg) at day 6 ( $p = 0.0009$ ), day 8 ( $p < 0.0001$ ), day 10 ( $p < 0.0001$ ) and day 12 ( $p < 0.0001$ ) post-injury. Similarly, 50 mg/kg and 100 mg/kg doses also showed significantly improved grip force ( $p = 0.007$ ) after injury (Figure 2 B). The improvement in motor function regain was also confirmed by

comparing the skeletal muscle mass ratio of all groups. Tibialis anterior (TA) and soleus muscles from both ipsi and contralateral legs of each animal were dissected and weighed to calculate a mass ratio. TA muscle is a major player, having a significant role in leg functions such as running, walking, and hiking, while the soleus muscle is the part of the calf muscles that aid in running, walking, and maintaining posture balance. The muscle mass ratio of both TA and soleus muscles was significantly improved in *F. asafaetida* chow groups. Particularly, 100mg and 200mg exhibited significant improvement in TA mass ratio ( $p = 0.002$ ) and also exhibited highly significant improvement in soleus muscle mass ratio ( $p = 0.0002$ ), (Figure 2 C and D).

### *F. asafaetida* hastens sensory function retrieval

The retrieval of sensory function was evaluated by observing paw withdrawal latency, following a thermal stimulus application. Abrupt paw withdrawal on exposure to hot surface indicates normal sensory functions, while a delay in this withdrawal represents dysfunctional sensory response. *F. asafaetida* chow group (200 mg/kg) displayed a significant decrease ( $P = 0.002$ ) in paw withdrawal latency on day 6 and day 9 post-injury. However, on day 9 post-injury, all *F. asafaetida* chow groups (50 mg, 100 mg, and 200 mg) displayed a significant decrease ( $P = 0.005$ ) in paw withdrawal latency time as compared to the control group (Figure 3).

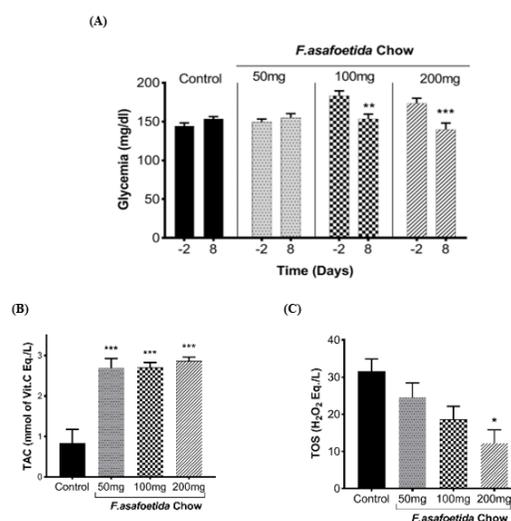


**Figure 3:** Effect of *F. asafaetida* on sensory function recovery. Results are mean  $\pm$  SEM; Measurement of paw withdrawal latency of mice served with normal chow (control  $n = 7$ ), *F. asafaetida* chow 50 mg ( $n = 7$ ), 100 mg ( $n = 7$ ) and 200 mg ( $n = 7$ ). Two-way repeated measure ANOVA, along with Tukey's multiple comparison test showed that *F. asafaetida* chow 200 mg significantly decreased the paw withdrawal latency time as compared to control on day 6 and 9 (\*\* $p = 0.002$ ) post-injury

### Influence of *F. asafaetida* on systemic indices

It is believed that glucose levels can modulate the equilibrium between anti-oxidative and oxidative progressions, and hyperglycemia-induced oxidative stress is an eminent factor for the development of numerous pathologies [14]. Here, *F. asafaetida* chow group (200 mg/kg) presented a highly significant amelioration ( $P = 0.0005$ ) in the glycemic level compared to that which was recorded before starting *F. asafaetida* supplementation (Figure 4 A). These observations are in accordance with reported data on the antidiabetic effects of this plant.

The TAC assay was carried out to measure the level of antioxidants in the biological samples. The addition of *F. asafaetida* to the feed significantly enhanced the TAC ( $P < 0.0001$ ) (Figure 4 B), and similarly, the TOS level was significantly reduced ( $P = 0.01$ ) in *F. asafaetida* chow (200 mg/kg) as shown in Figure 4 C.



**Figure 4:** Effect of *F. asafaetida* on glycemic and oxidative stress levels. Results are mean  $\pm$  SEM; (A) Measurement of glycemic level in mice served with normal chow (control  $n = 7$ ), *F. asafaetida* chow 50 mg ( $n = 7$ ), 100 mg ( $n = 7$ ) and 200 mg ( $n = 7$ ). The glycemic level was measured 2 days before, and then 8 days after inducing injury. Two-way repeated measure ANOVA along with Sidak's multiple comparisons tests showed a highly significant decrease in glycemic level for *F. asafaetida* chow 200 mg (\*\* $P = 0.0005$ ). (B) Total antioxidant capacity measured in mice as in A. One-way repeated measure ANOVA along with Tukey's multiple comparisons test showed highly significant differences (\*\* $p < 0.0001$ ) for all *F. asafaetida* chow groups. (C) Total oxidant status measured in animals as in A. One-way repeated measure ANOVA along with Tukey's multiple comparisons test presented significant differences (\* $P = 0.01$ ) for *F. asafaetida* chow 200 mg group

## DISCUSSION

The PNI is one of the most common and life-threatening conditions with a wide range of symptoms that affect a large number of young people worldwide. The situation appears worse in developing countries where violations of traffic rules are common. After an injury to the peripheral nerve, a cascade of the regulatory process commences to clear the damaged tissues and to initiate the nerve-repairing process. However, the rate of this process is so sluggish that it takes several weeks or even years to be accomplished. Meanwhile, the commencement of muscular atrophy causes further delay in function retrieval [15]. Therefore, speeding up the rate of nerve regeneration and associated function recovery is requisite before the onset of muscle atrophy. Despite the availability of extensive work on PNI and its related mechanisms, reliable treatments offering complete function recovery are still inadequate. Although neuroprotective properties of *F. asafotida* have already been investigated, there is no information of its effects on the process of function rehabilitation after PNI.

The *Ferula* genus belongs to the family, Umbelliferae, and they are taken as rich sources of beneficial bioactive compounds [16]. *Ferula asafotida* is used as an antihelminthic, antispasmodic, and carminative agent in Iranian folk medicine system [17]. It also exhibits relief in bronchitis, stomach ache, whooping cough, indigestion, and asthma [16]. Some other reports indicate that this plant also shows the potency to upsurge sexual hunger [18]. Based on these interesting data, the present study was intended to discover the role of *F. asafotida* in accelerating function retrieval following sciatic nerve injury. Generally, the addition of any material in animal feed may alter the smell and taste, and causes modified eating patterns. To elude the interference of such an ambiguous eating pattern, feed consumption and body mass were observed daily during the course of the trial. It was found that *F. asafotida* addition modified neither feed intake and nor body mass. The restoration of motor function is dependent on the speed of nerve regeneration and quantity of motor units elevating innervation to the target muscle. That becomes evident in improved SFI value and muscle grip strength. *F. asafotida* (200 mg/kg) treated animals manifested an early recovery both in motor and sensory aspects. Following an injury, electrical impulses are interrupted, which leads to muscle mass decline that can be restored on reinnervation. So, muscle mass ratio is a reliable parameter associated

with the determination of function recovery [10,19,20]. The mass of both TA and soleus muscles appeared remarkably improved in *F. asafotida* treated animals. Similarly, ameliorated sensory function was also observed at the early stage, and this effect was prominent at a higher dose of *F. asafotida* (200 mg/kg). These findings suggest that *F. asafotida* might be more effective in accelerating function recovery at higher doses.

In a study on rats, it has been reported that the aqueous extract of *F. asafotida* (oleo gum resins) exhibits an anti-hyperglycemic effect [21]. Moreover, another study showed that the *F. asafotida*, at both doses of 200 and 400 mg/kg body weight, presented anti-diabetic activity (decreased FBS levels) after 14 days of treatment [22]. The findings of this study indicate a similar effect of *F. asafotida* on the blood glucose on the 8<sup>th</sup> day of treatment.

It is believed that oxidative stress stands as a leading mediator of pathogenesis of all major diseases including nerve injury. Oxidative stress initiates the mitochondrial dysfunction and causes neuronal damage, apoptosis, neuro-inflammation, and demyelination, whereas lower TOS and higher TAC levels improve functional recovery following PNI [23]. *F. asafotida* also possesses significant antioxidant capacity in both *in-vitro* and *in-vivo* studies at 200 and 400 mg/kg doses [7,22]. Accordingly, the addition of *F. asafotida* in the feed of mice significantly up-regulated the TAC and attenuated the level of TOS. These findings are concomitant with the already documented characteristics of this plant. Based on these findings, it can be summed up that *F. asafotida* can prove an interesting drug candidate to combat the problem of injuries to the nervous system. Future extensive and detailed trials can unravel this mystery.

## CONCLUSION

The findings of the present work indicate that *F. asafotida* (oleo gum resin) has the potential to accelerate sensory motor functions regain following a mechanically induced insult to a peripheral nerve. *F. asafotida* exhibits remarkable advantages at a dose of 200 mg/kg. Further investigations are needed in this direction for the identification, isolation and characterization of bioactive molecule that actually bestows these observed effects.

## DECLARATIONS

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### Conflict of interest

The authors declare that no conflict of interest is associated with this work.

### Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. G.H, H.A., and A.R. designed the experiments and experimental design; S.K.S.K., A.R., and N.A., performed the experiments; G.H analyzed the data; K.S.U., S.A.M, and N.B. contributed reagents/materials/analysis tools; G.H and A.R actively participated in writing the draft of this manuscript.

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