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Amelioration of Paclitaxel Induced Neuropathy by *Gymnema sylvestre* in Wistar Rats

Shubhangi Hemraj Pawar, Anjalee Anil Gite and Rupali Arun Patil

Department of Pharmacology, Mahatma Gandhi Vidyamandir's Pharmacy College, Mumbai-Agra Road, Nashik 422003, Maharashtra, India

ABSTRACT

Background and Objective: Paclitaxel is commonly used taxane in the treatment of various solid tumors, developing symptoms of neuropathy in 60 to 90% of patients. *Gymnema sylvestre* has potent antioxidant and anti-inflammatory activity. So this study aims to assess its efficacy in paclitaxel-induced neuropathy and evaluate the effects of *Gymnema sylvestre* on behavioral, electrophysiological, biochemical, and histopathological changes in paclitaxel-induced neuropathy in Wistar rats. **Materials and Methods:** Wistar rats (n = 6) were divided into six groups. Neuropathy was caused by four injections of Paclitaxel (2 mg/kg, i.p) on alternate days. Treatment with *G. sylvestre* (100, 200, 400 mg/kg p.o.) and Gabapentin (300 mg/kg p.o.) started after the last paclitaxel injection for the next 4 weeks. Behavioral changes were assessed weekly. Motor nerve conduction velocity was studied at the end of treatment. After animal sacrifice, biochemical and histopathological studies were performed using sciatic nerve homogenate. Data are expressed as Mean±SEM and analyzed by one-way ANOVA with Dunnett's test using GraphPad Prism (v10.2.3), where *$p<0.05$. **Results:** Various doses of *G. sylvestre* significantly reversed the behavioral changes assessed by hot plate ($p<0.05$), cold plate ($p<0.01$), actophotometer ($p<0.05$) and von Frey filament ($p<0.01$), electrophysiological (Nerve conduction velocity with $p<0.01$), biochemical (MDA, GSH, SOD with $p<0.01$), and histopathological changes induced by paclitaxel in a dose-dependent manner. **Conclusion:** The *G. sylvestre* exhibits antioxidant, antihyperalgesic and neuroprotective effects and protects against paclitaxel-induced neuropathy. Thus *G. sylvestre* could be used as a new therapeutic approach along with current medicines in treating peripheral neuropathy.

KEYWORDS

Allodynia, chemotherapy, hyperalgesia, neuropathy, paclitaxel

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INTRODUCTION

Chemotherapeutic agents used in cancer treatment have neurotoxic effects leading to peripheral neuropathy[1] in 60 to 90% of individuals, leading to premature discontinuation of therapy[2,3]. The severity of symptoms of Chemotherapy-Induced Peripheral Neuropathy (CIPN) varies from individual to individual. In some cases, the severity of the symptoms may cause patients to reduce the dose or temporarily halt their treatment to alleviate discomfort. However, CIPN can continue even after chemotherapy has ended. Paclitaxel (PTX) is one of the most commonly used chemotherapeutic agents for treating solid tumors[4]. Various mechanisms have been identified that contribute to its neurotoxicity, including local degeneration of distal axons, alterations in mitochondrial ultrastructure and transport, increased neuroinflammation, and oxidative stress in the spinal cord and dorsal root ganglia (DRG)[5-7].

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The PTX-Induced Peripheral Neuropathy (PIPN) is a sensory neuropathy influenced by dosage, infusion duration, and other health factors. Symptoms, including numbness and tingling, typically start within 24 to 72 hrs. Patients suffer from chronic pain, loss of sensation, and allodynia, after "stocking and glove" symptoms, which collectively affect the quality of life of patients. Currently, for cancer patients, there is no cure or preventive treatment for PIPN, drug therapy can be given to alleviate symptoms[8,9]. Approximately 90% of paclitaxel-treated patients develop hyperalgesia and allodynia[10,11]. Paclitaxel increases oxidative stress and causes axonal degeneration, neuro-inflammation, and alterations in mitochondrial structure. Thus, many herbal drugs with antioxidant potential are screened and proven as neuroprotective. Herbal ingredients have been widely studied for their effectiveness in relieving PTX-induced pain. Natural plant components such as curcumin[12], resveratrol[13], gallic acid[14], puerarin[15], and naringin[16] have shown the ability to alleviate the discomfort associated with PTX. *Gymnema sylvestre*, one of the most powerful medicinal plants[17]. *Gymnema sylvestre* belongs to the Apocynaceae family and is an effective anti-inflammatory and antioxidant agent[18,19]. So this study aimed to assess its efficacy in paclitaxel-induced neuropathy and evaluate the efficacy of *Gymnema sylvestre* in paclitaxel-induced neuropathy by examining its effects on behavioral, electrophysiological, biochemical, and histopathological changes in Wistar rats.

MATERIALS AND METHODS

Study area: The current study was conducted at the Department of Pharmacology, MGVs Pharmacy College, Nashik, Maharashtra, India in the period of November, 2023 to March, 2024.

Research protocol: Paclitaxel (Inducer) was a gift sample from HCG Manavata Cancer Centre, Nashik, and Gabapentin (Standard drug) was a gift sample from Sun Pharma, India. *Gymnema sylvestre* powder was purchased from a local Ayurvedic supplier.

From the literature survey, minimum therapeutic doses of *G. sylvestre* were finalized as 100, 200, or 400 mg/kg/day orally. Standard drug Gabapentin 300 mg/kg/day p.o. was used to compare the results.

Thirty six animals were procured from LACSMI BIOFARMS Pvt. Ltd. (1277/PO/RcBt/S/09/CPCSEA) and divided into 6 groups (n = 6) and treated for 5 weeks (1 week for paclitaxel injections and the next 4 weeks for treatment).

- **Group I:** Normal, received the vehicle as saline only
- **Group II:** Diseased control (Paclitaxel 2 mg/kg, i.p.) on 4 alternate days
- **Group III:** Paclitaxel+*G. sylvestre* (100 mg/kg, p.o.) for next 4 weeks
- **Group IV:** Paclitaxel+*G. sylvestre* (200 mg/kg, p.o.) for next 4 weeks
- **Group V:** Paclitaxel+*G. sylvestre* (400 mg/kg, p.o.) for next 4 weeks
- **Group VI:** Paclitaxel+Gabapentin (300 mg/kg, p.o.) for next 4 weeks

Extraction procedure for *G. sylvestre*: The maceration process involved adding 70% ethanol to plant material in a 1:10 ratio. The sealed jars were shaken thoroughly and left at room temperature for 7 days, with twice-daily shaking. After 7 days, the mixture was filtered and the process was repeated if necessary. The filtrate was concentrated using a rotary evaporator (BUCHI-Rotavapor R-100) at 40-50°C under reduced pressure, resulting in a thick extract. This was dried in a vacuum oven at 40°C until a constant weight was achieved. The dried extract was weighed to determine the yield and stored in an airtight container at 4°C[20].

Phytochemical investigation: Phytochemical screening tests of extracts of *G. sylvestre* were carried out following the standard procedures to investigate the types of secondary metabolites present in the plant under investigation (Table 1). The presence of alkaloids was confirmed through Dragendorff's test, Mayer's test, Wagner's test, and Hager's test. The presence of carbohydrates was indicated by Fehling's test[21,22].

Table 1: Phytochemical screening tests and their respective results for *Withania somnifera* and *Gymnema sylvestre*

Phytochemical	Test name	Observation	Result
Alkaloids	Dragendorff's test	Orange-red precipitate forms	Alkaloids present
	Mayer's test	Creamy white precipitate forms	
	Wagner's test	Reddish-brown precipitate	
	Hager's test	Yellow precipitate forms	
Carbohydrates	Fehling's test	Red precipitate	Carbohydrates present
Glycosides	Keller-Killiani test	Reddish-brown ring at the junction	Glycosides present
Steroids	Salkowski test	Red color in chloroform layer	Steroids present
Saponins	Foam test	Stable foam	Saponins present
Tannins	Lead acetate test	White precipitate forms	Tannins present
Flavonoids	Lead acetate test	Yellow precipitate	Flavonoids present

Induction of peripheral neuropathy: Clinically formulated paclitaxel solution for infusion was diluted with 0.9% sterile saline to achieve a 2 mg/mL solution for injection. The animals received intraperitoneal injections of 2 mg/kg paclitaxel or an equivalent volume of the vehicle solution on four alternate days (days 0, 2, 4, and 6) and they were promptly returned to their home cages after each administration. Test drug treatment started from the last day of the paclitaxel injection schedule, considered as 0 weeks and treatment continued for the next 4 weeks[23].

Ethical consideration: The experimental protocol was approved by the Institutional Animal Ethical Committee of Mahatma Gandhi Vidyamandir's College of Pharmacy, Panchvati, Nashik. (MGV/PC/CPCSEA/XXXIX/01/2023-24/03, Date: 26/10/2023). The experiment adhered to CPCSEA guidelines.

Behavioural tests

Thermal hyperalgesia: Eddy's hot plate (Orchid Scientifics, India) maintained at 55±2°C was used to assess the thermal nociceptive threshold. Animals were individually tested by placing on the hot plate and paw-licking latency (sec) was recorded. A test cut-off time of 15 sec was enforced[23].

Cold allodynia: The animal was placed on the cooled plate (Orchid Scientifics, India) at 5°C and the time to induce nociceptive behavior indicated by shivering and paw licking was recorded as the response time[23].

Locomotor activity: An actophotometer test[24] was performed to assess the spontaneous motor behavior of the rodents. Each animal was observed for 5 min in a square closed field area (30×30×30 cm) equipped with 6 photocells. Interruptions of the photocell beam (locomotor/exploratory action) of rats were recorded by the digital counter (Orchid Scientifics, India).

Mechanical allodynia: Von Frey was developed by Physiologist Maximilian[23]. Von Frey filaments are used for the evaluation of mechanical allodynia in rats and mice. Rat was placed on wire mesh for easy application of Von Frey filaments and acclimatized for 5 to 10 min. Filament (von Frey hairs) was applied from below the mesh floor to the planter surface of the hind paw with sufficient force to cause slight bending against the paw and hold for sec. Immediate withdrawal of the left hind limb was considered a positive response. Observations were documented in the format OXXOXO, where O indicated-no withdrawal response and X indicates withdrawal response. This method of observation is up and down method of Dixon and the 50% g threshold is calculated by the formula:

$$50\%\ g\ threshold = 10\ E\ (xf+k\delta)/10,000$$

where, Xf is the log units of the last von Frey filament used; k is a tabular value for the pattern of positive/negative responses and δ is a Mean difference (in log units) between stimuli (0.224)[23].

Motor Nerve Conduction Velocity (MNCV): The MNCV recordings were carried out after the completion of treatment. Animals were anesthetized by Ketamine (90 mg/kg i.p.) and Xylazine (5 mg/kg i.p.). The MNCV assessment was conducted using an AD Instrument's 8-channel PowerLab with an animal nerve stimulating electrode (MLA0320) and needle electrodes (MLA1204). Action Potential was generated by applying a stimulating electrode at the proximal end and recording done from the distal end. The distance between the stimulating electrode and recording electrodes divided by the latent period was calculated as conduction velocity. The latent period is the time, elapsed between applications of stimulus until the peak of the maximum compound action potential[25].

Antioxidant studies

Estimation of GSH level: Estimation of reduced Glutathione (GSH) levels in the sciatic nerve 0.7 mL tissue homogenate was added to 2 mL 5% TCA. The mixture was centrifuged at 2500 rpm for 5 min. Then 3 mL 5 mM DTNB and 1 mL 10 mM phosphate buffer were added. The absorbance of the clear supernatant was measured at 412 nm. The GSH absorbance of the Normal group was considered as 100% and comparatively GSH (%) was calculated for test and standard groups and then GSH (%) of the diseased control group was subtracted from every treatment group and standard group to calculate the percentage of increase in GSH level[26,27].

Estimation of SOD level: Enzymatic activity levels of SOD in the supernatant of the sciatic nerve homogenate were measured. 0.5 mL tissue homogenate added to 0.3 M 0.5 mL sodium carbonate buffer having pH 10.2. 0.5 mL 0.6 mM EDTA was added to the above solution and centrifuged at 2500 rpm for 5 min. 1 mL distilled water was added to 0.5 mL supernatant, incubated for 10 min at RT then 0.5 mL, 1.8 mM epinephrine was added. The absorbance was measured at 480 nm. The SOD absorbance of the Normal group was considered as 100% and comparatively SOD (%) was calculated for test and standard groups then SOD (%) of the diseased control group was subtracted from every treatment group and standard group to calculate the percentage of increase in SOD level[26].

Estimation of MDA oxidative stress marker: The MDA was estimated in the sciatic nerve tissue homogenate. In brief, 1 mL tissue homogenate was mixed with 3 mL TBA:TCA:HCL solution and heated for 30 min at 90°C. Following cooling, centrifugation and absorbance of the supernatant were measured at 532 nm. The MDA absorbance of diseased control was considered as 100% (i.e., 0% inhibition of MDA) and comparatively MDA (%) calculated for test and standard groups. After that values of the treatment group and standard group were subtracted from 100 to calculate the final inhibition (%) of MDA. Absorbance is comparatively decreased and inhibition (%) is increased[26].

Histopathological assessment of the sciatic nerve: The isolated sciatic nerve was kept in the 10% formalin. A histopathological study was done at Karmaveer Bhausaheb Hiray Dental College and Hospital, Nashik. Staining was done by using hematoxylin and eosin. Sections observed under light microscope (10×10) (Coslab, India)[27].

Statistical analysis: Data is expressed as Mean±SEM; analyzed by one-way ANOVA followed by Dunnett's Multiple Comparison Test (compared with the control group) analyzed by using Graph Pad Prism version 10.2.3. The *$p<0.05$, **$p<0.01$, and ***$p<0.001$ are considered to be significant denoted as the letter a in comparison to normal and b in comparison to the diseased control group.

RESULTS

Phytochemical analysis: Results of phytochemical screening tests of *G. sylvestre* are shown in Table 1. The phytochemical analysis revealed the presence of several bioactive compounds. Alkaloids were confirmed by positive results in Dragendorff's test (orange-red precipitate), Mayer's test (creamy white precipitate), Wagner's test (reddish-brown precipitate), and Hager's test (yellow precipitate). Carbohydrates were indicated by the formation of a red precipitate in Fehling's test. Glycosides showed

a positive result with the Keller-Killiani test, evident by the formation of a reddish-brown ring at the junction. Steroids were detected through the Salkowski test, which produced a red color in the chloroform layer. Saponins were present as indicated by the formation of stable foam in the foam test. Tannins were confirmed by a white precipitate in the lead acetate test, while flavonoids were verified through the formation of a yellow precipitate in the same test.

Behavioural studies

Effect of *G. sylvestre* on heat hyperalgesia (hot plate method) in diseased control and treatment animals: Paw withdrawal latency and the jumping response were observed weekly, after placing the animal on a preheated plate (55°C). Thermal hyperalgesia was found to be produced in the diseased control group from 2nd week of paclitaxel injection. A significant decrease ($p<0.01$) in time was observed from 2nd week in group II (Diseased control) animals compared to group I (Normal). Changes in the onset of paw withdrawal observed in groups III, IV, and V are statistically significant ($p<0.05$) and in group VI ($p<0.01$) compared to group II animals (Fig. 1).

Effect of *G. sylvestre* on cold allodynia (cold plate method) in diseased control and treatment animals: Cold allodynia in animals was evaluated by using a cold plate test at a temperature of 5°C and the time required for onset of paw withdrawal was measured in seconds. Cold allodynia was found to be produced in the diseased control group from 2nd week of paclitaxel injection. A significant decrease ($p<0.01$) in time was observed from 2nd week in group II animals compared to group I. Changes in the onset of shivering observed in groups III, and IV, are statistically significant ($p<0.05$) and in groups V and VI ($p<0.01$) compared to group II animals (Fig. 2).

Effect of *G. sylvestre* on locomotor activity score (actophotometer) in diseased control and treatment animals: An actophotometer test was performed to assess the spontaneous motor (exploratory) behavior of the rodents with an actophotometer. A significant decrease ($p<0.01$) in locomotor activity score was found in the diseased control group from 2nd week of paclitaxel injection compared to group I (Normal). Changes in locomotor activity score on actophotometer in 5 min observed in groups III, and IV, are statistically significant ($p<0.05$) and groups V and VI ($p<0.01$) compared to group II animals (Fig. 3).

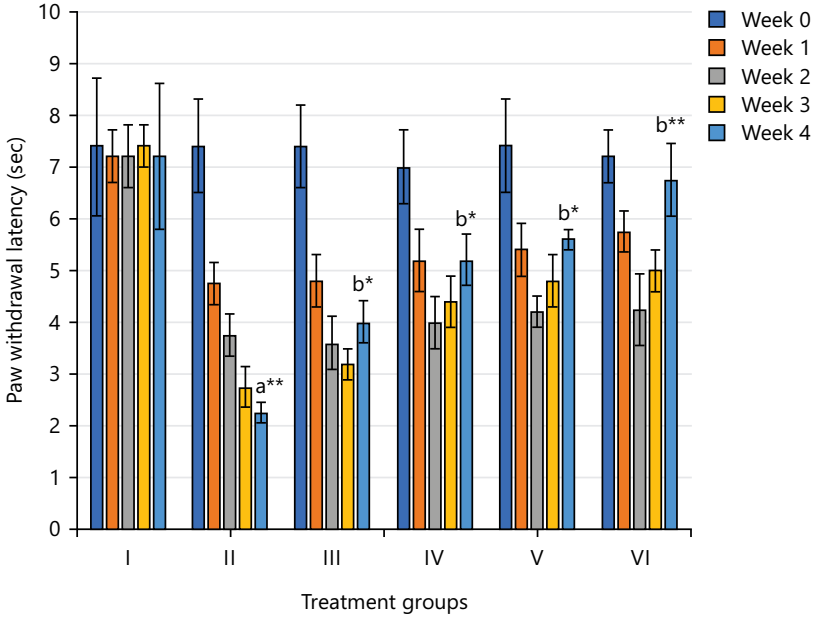

Fig. 1: Effect of various doses of *G. sylvestre* on heat hyperalgesia evaluated by hot plate test in diseased control and treatment animals

*p<0.05, **p<0.01 and ***p<0.001 considered to be significant denoted as letter a in comparison to normal and b in comparison to diseased control group

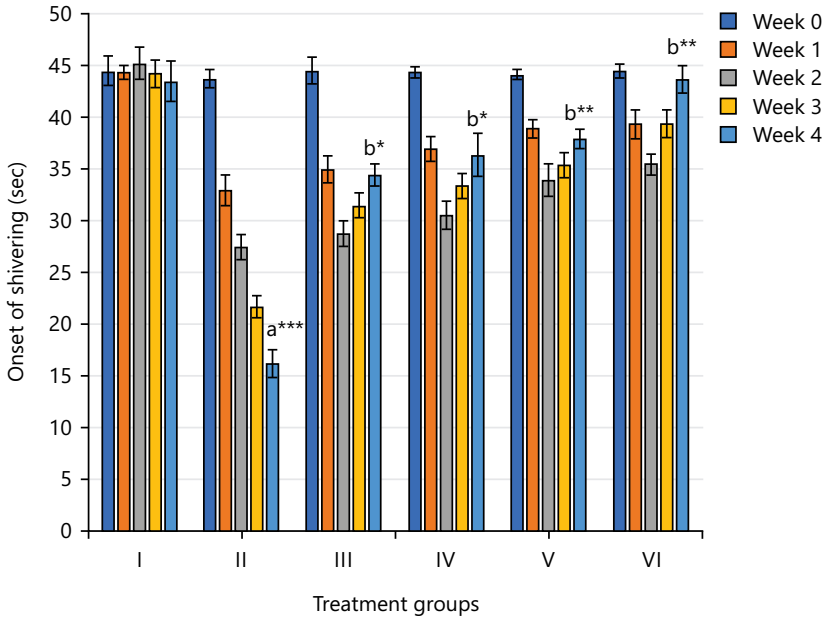

Fig. 2: Effect of various doses of *G. sylvestre* on cold allodynia evaluated by cold plate test in diseased control and treatment animals

*p<0.05, **p<0.01 and ***p<0.001 considered to be significant denoted as letter a in comparison to normal and b in comparison to diseased control group

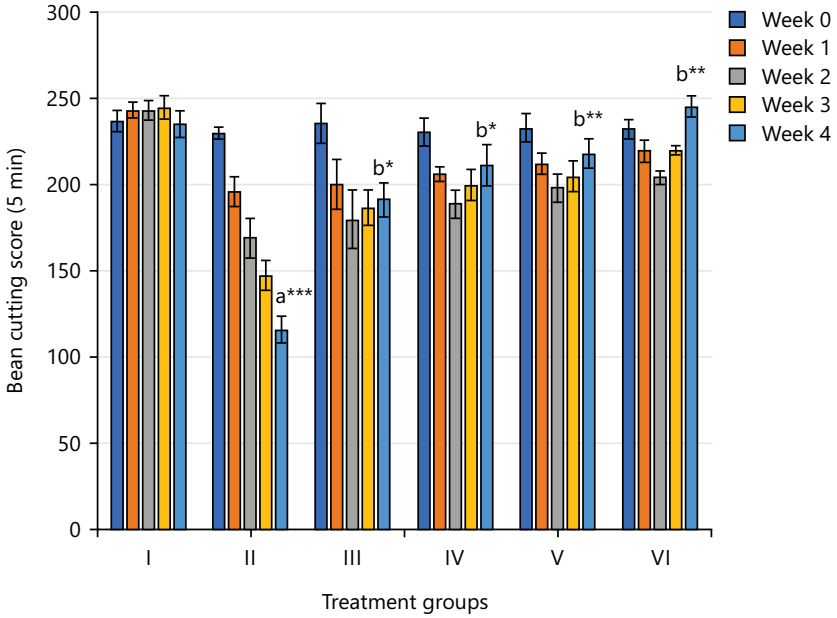

Fig. 3: Effect of various doses of *G. sylvestre* on locomotor activity score evaluated by actophotometer test in diseased control and treatment animals

*p<0.05, **p<0.01, and ***p<0.001 are considered to be significant denoted as letter a in comparison to normal and b in comparison to the diseased control group

Effect of *G. sylvestre* on mechanical allodynia (Von Frey Filament) in diseased control and treatment animals: In the diseased control group mechanical allodynia was observed from 1st week of paclitaxel injection indicated by withdrawal response to minimum force of filament and thus decrease in 50% g threshold. A significant decrease ($p<0.01$) in time was observed from 2nd week in group II animals compared to group I. Changes in mechanical allodynia (50% g threshold) on Von Frey Filament observed in groups III, IV, V, and VI are statistically significant ($p<0.01$) compared to group II animals (Fig. 4).

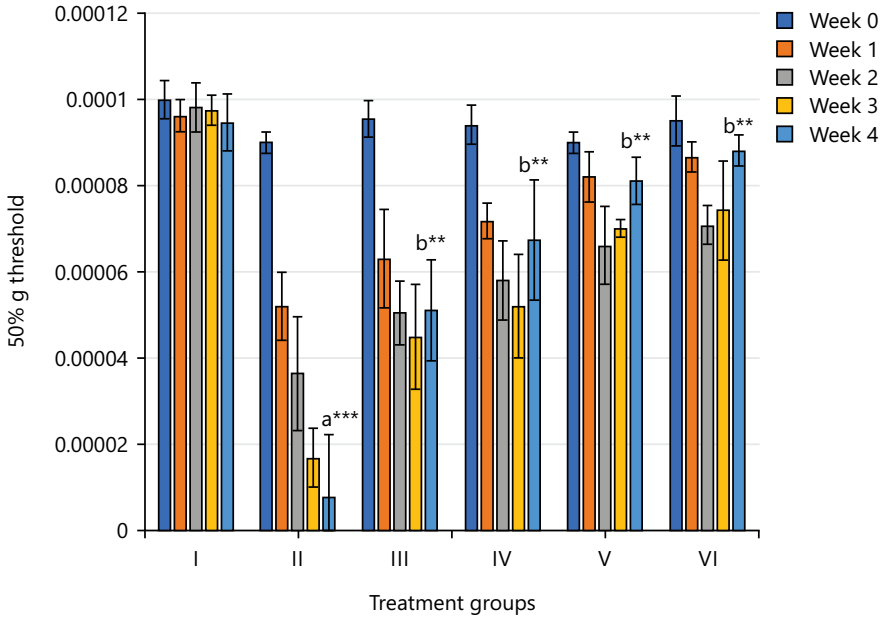

Fig. 4: Effect of various doses of *G. sylvestre* on mechanical allodynia evaluated by Von Frey Filament test in diseased control and treatment animals

*p<0.05, **p<0.01, and ***p<0.001 are considered to be significant denoted as letter a in comparison to normal and b in comparison to the diseased control group

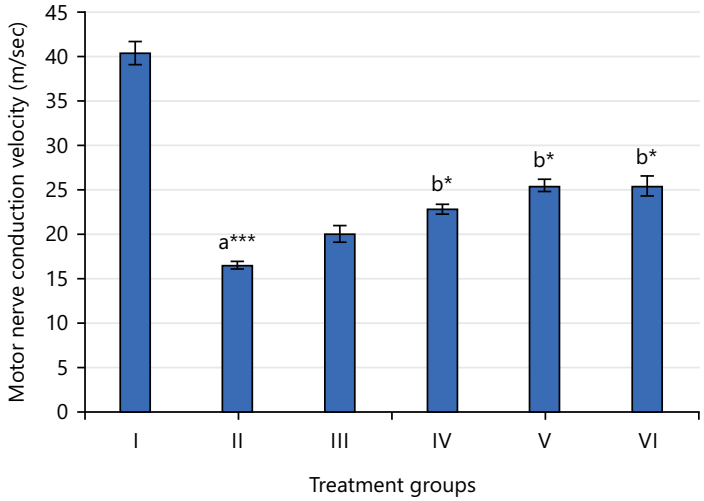

Fig. 5: Effect of various doses of *G. sylvestre* on nerve conduction velocity in diseased control and treatment animals

*p<0.05, **p<0.01 and ***p<0.001 are considered to be significant denoted as letter a in comparison to normal and b in comparison to the diseased control group

Nerve conduction velocity: After completion of 4th week's treatment, MNCV (m/sec) was measured. Diseased control animals have shown a marked reduction in conduction velocity compared to normal animals. This indicates neuronal damage which is protected in treatment groups. Changes in conduction velocity observed in groups IV, V, and VI ($p<0.05$) are statistically significant compared to group II animals (Fig. 5).

Antioxidant studies

Reduced glutathione (GSH): The GHS is the primary antioxidant in the cell. A significant decrease in the amount of GHS was observed in group II as compared with group I. Treatment with *G. sylvestre* group V

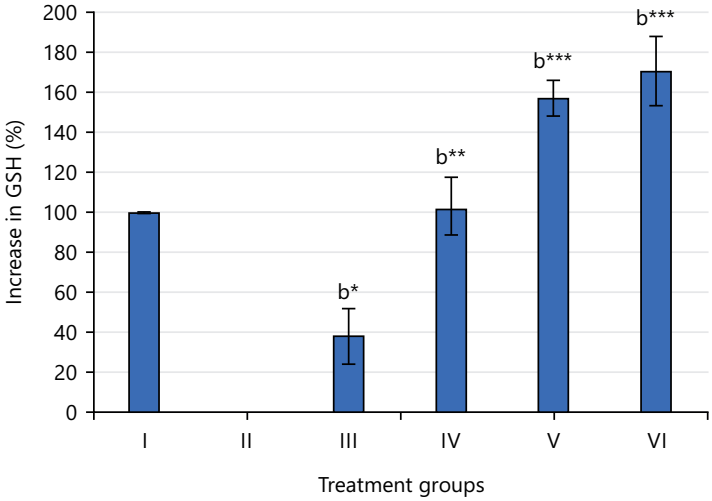

Fig. 6: Effect of various doses of *G. sylvestre* on increase in GSH (%) in diseased control and treatment animals

*p<0.05, **p<0.01, and ***p<0.001 are considered to be significant denoted as letter a in comparison to normal and b in comparison to the diseased control group

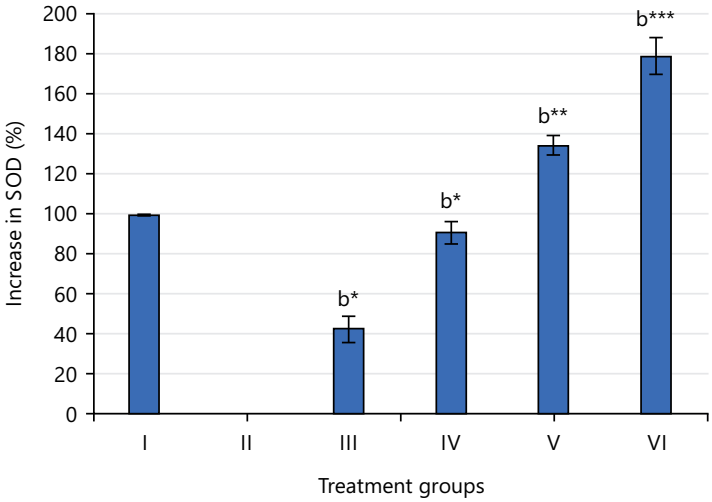

Fig. 7: Effect of various doses of *G. sylvestre* on increase in SOD (%) in diseased control and treatment animals

*p<0.05, **p<0.01, and ***p<0.001 are considered to be significant denoted as letter a in comparison to normal and b in comparison to the diseased control group

and treatment with Gabapentin group VI showed a significant increase (p<0.001) in GSH level as compared to group II. Group IV showed a significant increase (p<0.01) in GSH level as compared to group II. As compared to group II GSH level of group III significantly increased with a p<0.05 (Fig. 6).

Superoxide dismutase (SOD): The SOD is a crucial enzyme in the defense against oxidative stress. A significant decrease in SOD levels was observed in group II (diseased control) compared with group I (normal). Treatment with Gabapentin in group VI showed a significant increase (p<0.001) in SOD levels compared with group II. Group V showed a significant increase (p<0.01) in SOD levels compared with group II. In comparison to group II, the SOD levels in groups III, IV significantly increased with a p<0.05 (Fig. 7).

Malondialdehyde (MDA): The MDA was measured from sciatic nerve tissue homogenate and absorbance was recorded at 532 nm. Oxidative stress is found to be increased in group II indicated by increased absorbance. Absorbance is comparatively decreased and percentage of inhibition is increased significantly (p<0.01) by *G. sylvestre* and Gabapentin treatment (Fig. 8).

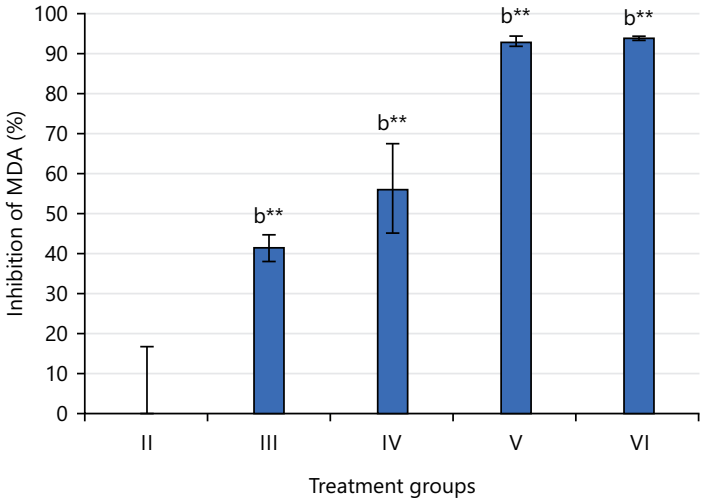

Fig. 8: Effect of various doses of *G. sylvestre* on percentage of inhibition in MDA in diseased control and treatment animals

*p<0.05, **p<0.01, and ***p<0.001 are considered to be significant denoted as letter a in comparison to normal and b in comparison to the diseased control group

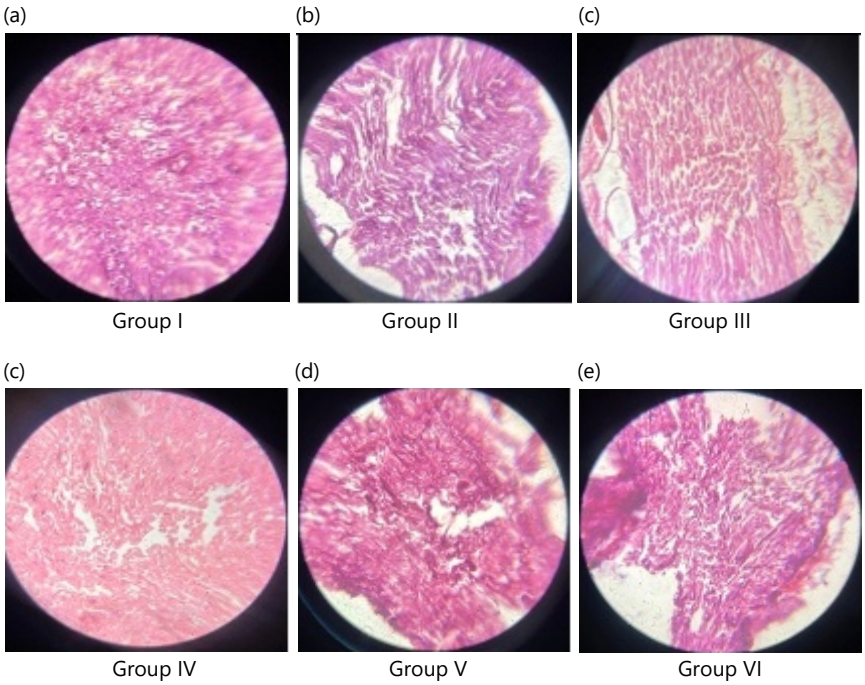

Fig. 9(a-e): Histopathology section of H and E-stained sciatic nerve of normal group, diseased control group, test group and standard group

Group I: Vehicle treated, Group II: Diseased control, Group III: *Gymnema sylvestre* 100 g/kg, p.o, Group IV: *Gymnema sylvestre* 200 mg/kg, p.o., Group V: *Gymnema sylvestre* 400 mg/kg, p.o., Group VI: Gabapentin 300 mg/kg, p.o.)

Histopathology: Isolated sciatic nerve kept in the 10% formalin. A histopathological study was done at KBH Dental College and Hospital, Nashik. Histopathology Sections of H and E-stained sciatic nerve of diseased control rats showed epineuronal edema and infiltration of neutrophils around blood vessels and swelling of nerve fibres compared to the normal group. Treatment with *G. sylvestre* and Gabapentin showed mild edema few infiltrating neutrophils around blood vessels and minor swelling of nerve fibers. Group 1-VI (Fig. 9).

DISCUSSION

Paclitaxel is one of the most commonly used therapies for solid tumors. However, its use is frequently linked to the development of peripheral neuropathy and neuropathic pain, which can sometimes cause patients to lower the dosage or even discontinue treatment[4]. Hyeralgesia and allodynia are common symptoms observed in neuropathy. In this study, thermal hyperalgesia was assessed by the hot plate method[23]. *Gymnema sylvestre* treatments were evaluated by measuring paw withdrawal latency and jumping responses. The heating surface allows stimulation of A or C thermal nociceptors in rats, resulting in decreased pain threshold and withdrawal latency which was observed in group II (diseased control). *Gymnema sylvestre* has shown to a significant increase in paw withdrawal time in a dose-dependent manner which may be associated with decreased stimulation of A or C fibers which means a decrease in thermal hyperalgesia. The cold plate test at 5°C was used to evaluate the effect of *G. sylvestre* in mitigating cold allodynia in rats with paclitaxel-induced neuropathy[23]. Cold stimuli activate neuronal Na^+ channels and cause the release of neurotransmitters (substance P, glutamate, and calcitonin gene-related peptide) involved in pain transmission and modulation within the nervous system mediated through pre-synaptic Ca^{++} channels. These ion channels are specifically localized on small, unmyelinated C-fibres. Skin cooling activates thermo receptors and further activates C and A-fibers to produce allodynia. This cold allodynia was found to be attenuated significantly with *G. sylvestre* treatment in a dose-dependent manner. Locomotor activity score in rats was evaluated using an actophotometer[24]. Paclitaxel disrupts microtubules by binding with beta-tubulin subunits, disrupting axonal transport and causing sensory and motor nerve damage. This leads to hypersensitivity in sensory neurons and functional deficits in motor neurons, ultimately impairing coordination and locomotor activity[28]. The diseased control group showed a significant reduction in locomotor activity 4 weeks of treatment with *G. sylvestre* and Gabapentin LED to a significant improvement in locomotor activity by restoring axonal transport in nerve cells[23]. Research studies have shown that paclitaxel induces mechanical allodynia by microtubule disruption, mitochondrial dysfunction, and increasing ROS production, which contributes to neuronal hyperexcitability, resulting in a lowered mechanical threshold[29]. This study revealed that *G. sylvestre* significantly improved mechanical allodynia in rat paclitaxel-induced neuropathy but in dose-dependent manners. The highest dose nearly restored the normal threshold, meaning a decrease in mechanical allodynia. After completion of 4 weeks of treatment, Nerve Conduction Velocity (NCV) was measured with the help of distance (m) between two electrodes and latency period (sec)[25]. Paclitaxel induces mitochondrial dysfunction in sciatic nerve cells, which decreases ATP production needed for maintaining ion channel activation[30]. Paclitaxel also causes demyelination of nerve cells resulting in loss of axonal integrity, reducing the nerve's ability to conduct electrical impulses efficiently, and decreasing NCV in the sciatic nerve of rats[31]. The study found that paclitaxel significantly reduced NCV in Wistar rats, indicating nerve damage. NCV was found to be increased significantly with the 4 weeks treatment of *G. sylvestre* in a dose-dependent manner probably by preventing demyelination. Treatment with Gabapentin also increased NCV significantly. As per results obtained in this study, decreased levels of GSH, SOD, and increased MDA were observed in paclitaxel treatment. In paclitaxel-induced neuropathy, stabilization of microtubules contributes to mitochondrial damage and dysfunction in the sciatic nerve, characterized by increased production of reactive oxygen species (ROS) and increased oxidative stress which further damages cellular structures and impair mitochondrial function. Normally, antioxidant enzymes like GSH and SOD help to neutralize ROS and protect cells from oxidative damage. But in paclitaxel-induced neuropathy, the increasing ROS production decreases GSH and also inhibits SOD activity, reducing the cell's antioxidant defense. The elevated ROS levels cause lipid peroxidation. This process generates MDA as a byproduct, a marker of oxidative stress and lipid peroxidation. Accumulation of MDA leads to further neuronal damage and inflammation which causes neuropathic pain. The previous study of Wang *et al.*[32] found that *G. sylvestre* and Gabapentin significantly improved antioxidant enzymes (GSH and SOD) and reduced oxidative stress marker (MDA) in paclitaxel-induced neuropathy by restoring mitochondrial functions, indicating enhanced antioxidant defense. Histopathological examination of the sciatic nerve revealed significant nerve damage in

paclitaxel-treated rats, including neuronal edema, neutrophil infiltration, and nerve fiber swelling. Treatment with *G. sylvestre* and Gabapentin reduced these histopathological changes, suggesting their potential in protecting nerve tissue and managing chemotherapy-induced neuropathy. Thus, *G. sylvestre* has neuroprotective effect obtained through its anti-hyperalgesic, antioxidant, and anti-inflammatory actions. This plant extract is effective in managing neuropathy and could complement existing treatments.

CONCLUSION

Treatment with *G. sylvestre* over four weeks significantly improved behavioral changes (thermal hyperalgesia, cold allodynia, locomotor activity, and mechanical allodynia) and increased nerve conduction velocity. Additionally, this treatment reduced oxidative stress markers and increased antioxidant enzyme levels in a dose-dependent manner. Histopathological studies also revealed the neuroprotective activity of *G. sylvestre* in neuropathic pain. The results suggest that *G. sylvestre* has neuroprotective effects which are attributed to its anti-hyperalgesic, antioxidant, and anti-inflammatory properties, making it a promising candidate for treating paclitaxel-induced neuropathy along with existing therapies.

SIGNIFICANCE STATEMENT

Development of peripheral neuropathy after long use of paclitaxel in chemotherapy leads to discontinuation of treatment. Natural remedies offer safer alternatives to allopathy medicines with minimal side effects. So in current research work, *Gymnema sylvestre* was used against paclitaxel-induced neuropathy. The results indicated that *G. sylvestre* exhibits antioxidant, antihyperalgesic, and neuroprotective effects and protects paclitaxel-induced neuropathy in a dose-dependent manner. Thus *G. sylvestre* could be used as a new therapeutic approach along with current medicines in treating peripheral neuropathy.

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