e-ISSN: 2320-4230, p-ISSN: 2961-6085

Journal of Drug Discovery and Therapeutics

Available Online at www.jddt.in

CODEN: - JDDTBP (Source: - American Chemical Society)

Volume 14, Issue 02; 2026, 1-8

Neuroprotective Effects of *Momordica charantia* Methanolic Root Extract Against Vincristine-Induced Peripheral Neuropathy in Rats: Behavioral, Biochemical, and Histological Evidence

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Received: 14-01-2026 / Revised: 20-02-2026 / Accepted: 26-03-2026
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Conflict of interest: No conflict of interest.

Abstract:

Vincristine-induced peripheral neuropathy (VIPN) is a debilitating complication of chemotherapy characterized by pain, sensory loss, and oxidative stress. This study evaluated the neuroprotective potential of methanolic extracts of Momordica charantia roots in a rat model of VIPN. Rats were administered vincristine (100 µg/kg/day i.p.) to induce neuropathy and treated with low (100 mg/kg) and high (200 mg/kg) doses of M. charantia extract or Methylcobalamin (50 µg/kg i.p.). Behavioral outcomes including thermal hyperalgesia (hot-plate and tail-flick), cold allodynia (acetone test), and nerve conduction velocity (NCV) were assessed. Pro-inflammatory cytokines (IL-6, IL-1β, TNF-α) and oxidative stress markers (LPO, SOD, CAT, NO) were measured biochemically. Sciatic nerve histopathology was performed. Vincristine produced significant neuropathic pain, increased cytokines, oxidative stress, and decreased NCV. Treatment with M. charantia mitigated pain behaviors, reduced inflammatory cytokines and oxidative stress, improved NCV, and preserved nerve architecture. These findings suggest that M. charantia extract exerts neuroprotective effects against VIPN possibly via antioxidant and anti-inflammatory mechanisms, supporting its therapeutic potential in chemotherapy-induced neuropathy.

Keywords: Momordica charantia; vincristine; peripheral neuropathy; oxidative stress; pro-inflammatory cytokines; nerve conduction velocity; neuroprotection

Introduction:

Chemotherapy-induced peripheral neuropathy (CIPN) is a common dose-limiting adverse effect of several anticancer agents, including vincristine, presenting as sensory loss, pain, and functional deficits that significantly impair quality of life. VIPN is associated with hyperalgesia, allodynia, reduced nerve conduction velocity, increased oxidative stress, and elevated pro-inflammatory cytokines such as TNF-α and IL-6 in peripheral nerve tissues.

Current clinical treatments provide limited relief, prompting investigation into alternative therapies. Natural products with antioxidant and anti-inflammatory properties have shown promise in alleviating neuropathic pain and nerve damage. Momordica charantia (bitter melon), a

medicinal plant of the Cucurbitaceae family, is widely recognized for its antioxidative, anti-inflammatory, and neuroprotective effects in various models of oxidative stress and neuropathy.

Previous studies demonstrated that standardized M. charantia fruit extract can attenuate vincristine-induced neuropathic pain through modulation of nitric oxide, GABAergic pathways, and antioxidant systems. However, the neuroprotective potential of methanolic root extracts in VIPN has not been fully explored. The present study aimed to assess the effects of methanolic M. charantia root extract on pain behaviors, NCV, pro-inflammatory cytokines, oxidative stress markers, and histopathological changes in a rat model of vincristine-induced peripheral neuropathy.

Materials and method

Collection and extraction

Fresh roots of Momordica charantia were collected from Alwar, Rajasthan. The roots were shade-dried at room temperature for seven days, pulverized, and sieved (coarse 10/40). Methanolic extract was prepared using a Soxhlet extractor with 250 g batches of powdered root. The extract was filtered, concentrated on a rotary evaporator at 55°C, and dried under vacuum.

Vincristine sulphate (Cytocristin®, 1 mg/1 mL; Cipla) and methylcobalamin injection (Methylcobal®; Eisai, Wockhardt Ltd.) were procured commercially. Methanol (Fisher Scientific) and ethanol (SD Fine Chem) were used as solvents. Analytical reagents—including Molisch's reagent, sulfuric acid, ferric chloride, sodium hydroxide, hydrochloric acid, carbonate buffer, DMSO, sodium carbonate buffer, TCA, chloroform, and NaCl—were obtained from Qualigens (Thermo Fisher Scientific, India). Mayer's reagent, L-ascorbic acid, thiobarbituric acid (TBA), and Griess reagent were purchased from Loba Chemie (Mumbai). Glacial acetic acid was sourced from Fisher Scientific, while copper sulphate, acetone, Tween-20, phosphate buffer, acetic anhydride, and ammonia solution were obtained from Merck (India). All other chemicals were of analytical reagent (AR) grade.

Experimental Animals:

Male Wistar rats (8–10 weeks, 150–200 g) and female Albino mice (8–10 weeks, 20–25 g) were used. Animals were acclimatized for one week in a fully ventilated room under a 12:12 h light/dark cycle at 25 ± 2°C, with free access to standard chow and water. All procedures were approved by the Institutional Animal Ethics Committee (IAEC) and conducted according to standard guidelines.

Acute Toxicity Study:

Acute oral toxicity of Momordica charantia methanolic extract was assessed according to OECD guideline 425. Animals were fasted overnight, and a limit test was performed starting at 2000 mg/kg. Doses of 175, 550, 1750, and 5000 mg/kg were tested sequentially. High and low doses for pharmacological studies were set at 1/10th and 1/20th of 2000 mg/kg, respectively, and prepared in Milli-Q water.

Pharmacological Evaluation in Vincristine-Induced Peripheral Neuropathy (VIPN):

Peripheral neuropathy was induced by intraperitoneal injection of vincristine (100 µg/kg/day) for 14 days. Rats were divided into five groups (n=6 per group):

- **Group 1:** Normal control (vehicle, saline)
- **Group 2:** Neuropathy control (vincristine 100 µg/kg/day)
- **Group 3:** Standard treatment (methylcobalamin, 50 µg/kg/day)

- **Group 4:** Low-dose M. charantia extract (100 mg/kg/day, p.o.)
- **Group 5:** High-dose M. charantia extract (200 mg/kg/day, p.o.)

Treatments were administered for 21 days following neuropathy induction.

Pain Sensation Tests:

- **Hot-plate method:** Rats were placed individually on a hot plate at 55°C. Paw licking or jumping was recorded as the endpoint, with a cutoff of 15 s to avoid tissue damage. Baseline responses were recorded before treatment.
- **Tail-flick method:** Rats' tails were preconditioned in 29°C water for 30 min, then immersed in 49°C water. The latency to tail-flick was measured three times, and the average was recorded.

Cold Allodynia (Acetone Spray Test):
100 µL of acetone was applied to the plantar surface of the left hind paw. Withdrawal responses were recorded over five trials, with 3–5 min intervals. The frequency of withdrawal responses was calculated as:

Withdrawal frequency (%)
=Number of paw withdrawals
Number of trials×100\text {Withdrawal frequency (\%)} = \frac {\text {Number of paw withdrawals}}{\text {Number of trials}} \times 100Withdrawal frequency (%)
=Number of trials
Number of paw withdrawals×100

Nerve Conduction Velocity (NCV):

Under anesthesia, the back of the rats was shaved. The left sciatic-tibial nerve was stimulated proximally at the sciatic notch and distally at the knee using bipolar electrodes. Compound muscle action potentials (CMAPs) were recorded from the ankle via unipolar electrodes. NCV (m/s) was calculated as the distance between stimulation sites divided by the difference in proximal and distal latencies.

Pro-inflammatory Cytokines:

Serum levels of IL-6, IL-1β, and TNF-α were measured using ELISA. Plates were coated with 100 µL of primary antibodies (2.5 µg/mL) in carbonate buffer (pH 9.6) and incubated overnight at 4°C. After washing and blocking with BSA, standards and samples were added. After incubation with HRP-conjugated secondary antibodies, TMB substrate was added, and absorbance was measured at 450 nm. Cytokine concentrations were determined from standard calibration curves.

Antioxidant Assays:

- **SOD:** Tissue supernatant was incubated with sodium carbonate buffer and EDTA. Adrenaline was added to initiate the reaction, and absorbance was measured at 480 nm. Activity expressed as units/min/mg protein.
- **Lipid peroxidation (MDA):** Tissue samples were treated with ferric chloride and L-ascorbic acid in phosphate buffer. After reaction with TCA and TBA and boiling, absorbance was measured at 532 nm. Results expressed as nmoles MDA/g protein.
- **Catalase (CAT):** Tissue supernatant was added to phosphate buffer and H_2O_2. The change in absorbance at 240 nm for 3 min was recorded. Results expressed as nmoles H_2O_2/min/mg protein.
- **Nitric oxide (NO):** Tissue samples were mixed with Griess reagent, incubated in the dark for 30 min, and absorbance measured at 548 nm. Values expressed as µmoles/g protein.

Histopathology:

Rats were euthanized using a high dose of pentobarbital. Bilateral sciatic nerves were

collected, and 1 cm tissue segments were fixed in 10% formalin. Samples were dehydrated, embedded in paraffin, sectioned at 5 µm, and stained with H&E and Luxol fast blue to assess neuronal damage and myelination.

Statistical Analysis:

Data are expressed as mean ± SEM (n=6). Statistical significance was assessed using one-way ANOVA followed by Tukey's test. Differences were considered significant at $p < 0.05$.

Results and discussion

Acute Toxicity Study:

No mortality was observed in the acute toxicity study up to a dose of 2000 mg/kg for methanolic extract of Momordica charantia roots. Doses of 1/20th and 1/10th of 5000 mg/kg (100 mg/kg and 200 mg/kg) were selected as low and high doses for pharmacological screening. Drugs were prepared by dissolving in Milli-Q water, and further studies were carried out.

Pharmacological Effects in Vincristine-Induced Peripheral Neuropathy (VIPN):

The pharmacological effects of methanolic extracts of Momordica charantia roots were studied in rats after administration of vincristine (100 µg/kg/day, i.p.), Methylcobalamin (50 µg/kg, i.p.), and methanolic extracts of M. charantia (100 mg/kg and 200 mg/kg, p.o.) in neuroprotective models.

Pain-Sensation Effect of VIPN in Rats:

Hot-Plate Method:

Vincristine-treated neuropathy control rats showed a significant increase ($p<0.001$) in hot-plate response time compared to normal control. Rats treated with M. charantia extract at high and low doses showed a significant improvement in response time ($p<0.001$ and $p<0.01$, respectively) compared to the standard Methylcobalamin control.

Tail-Flick Method:

Tail-flick latency was significantly higher in vincristine neuropathy control rats compared to normal control ($p<0.001$). Rats treated with M. charantia extract at high and low doses showed significant reduction in latency ($p<0.001$ and $p<0.01$, respectively) compared to Methylcobalamin control, indicating improved pain response.

Cold Allodynia – Acetone Spray Method:

Vincristine neuropathy control rats showed a significantly higher withdrawal frequency compared to normal controls. Treatment with methanolic extracts of M. charantia reduced the withdrawal frequency, indicating attenuation of cold allodynia compared to neuropathy control.

Measurement of Nerve Conduction Velocity (NCV):

Peripheral neuropathy is characterized by a decrease in NCV. After treatment with Methylcobalamin and low and high doses of methanolic extracts of Momordica charantia, NCV was measured (Figure1 d). Neuropathy control rats showed a significant reduction in NCV compared to normal controls ($p<0.001$). Treatment with Methylcobalamin and M. charantia extracts significantly improved NCV compared to the neuropathic group ($p<0.001$).

Estimation of Pro-Inflammatory Cytokines (IL-6, IL-1β, TNF-α):

The anti-inflammatory activity of methanolic extracts of Momordica charantia roots and Methylcobalamin was assessed. Vincristine-treated neuropathy control rats showed a significant increase in serum levels of IL-6, IL-1β, and TNF-α compared to normal controls. Treatment with M. charantia extracts and Methylcobalamin significantly reduced the production of these

cytokines compared to the neuropathy control group.

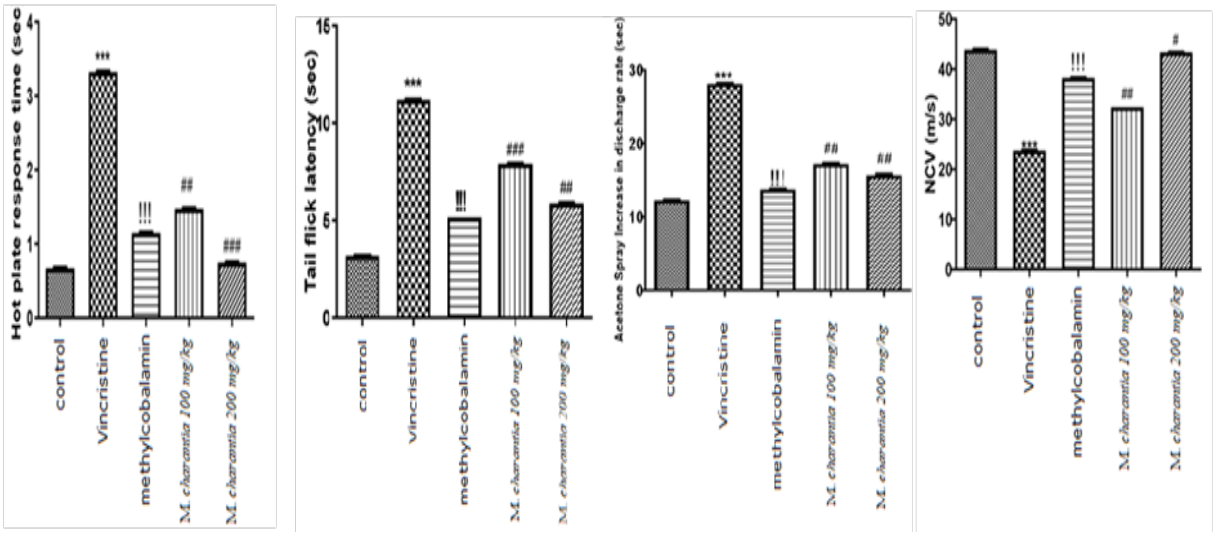

Figure 1 a) Pain-Sensation Effect of VPN In rats using Hot-Plate Method b) Pain-Sensation Effect of VPN In rats using Tail c) Cold Allodynia-Acetone Spray Test d) Measurement of Nerve Conduction Velocity (NCV)

Table 1: Estimation of pro-inflammatory cytokines e.g. IL-6, IL-1beta and TNF-alpha

S.No. No.	GroGroupsp	IL-6(µg/ml)	IL-beta(µg/ml)	TNF-alpha(µg/ml)
1	Normal control	231.6±2.27	138.2±2.32	187.6±2.86
2	Vincristine 100µg/kg/day i.p.	619.4±2.15***	489.4±2.17***	647.8±2.55***
3	Methylcobalamin 50µg/kgi.p.	441.7±2.134!!!	388.3±5.226!!!	463.5±2.593!!!
4	Mormordica charantia 100mg/kg,P.O.	528.7±4.68###	451.7±4.36###	541.9±2.06###
5	Mormordica charantia 200mg/kg,P.O.	341.7±2.14###	288.3±5.26###	363.5±2.53###

Values are expressed as Mean ± S.E.M (n=6). ***p < 0.001 compared to normal control; !!!p < 0.001 compared to disease control; ###p < 0.001 compared to standard Methylcobalamin control.

Assessment of Antioxidant Effect:

In vincristine-induced neuropathy, LPO and NO levels were significantly increased, while SOD and CAT activities were significantly decreased compared to normal controls ($p<0.001$). Treatment with methanolic extracts of Momordica charantia roots and Methylcobalamin significantly reduced LPO and NO levels ($p<0.001$) and restored SOD and CAT activities compared to the disease control group (Table 6.7).

Table 2: Antioxidant parameters including SOD, LPO, CAT, and NO.

Sl. No.	Group	SerumSOD (units/min/ mgof protein)	Serum LPO (nMoles ofMDA/g protein)	Serum CAT (nmolesH2O2/min/mg Protein	Serum NO(µmols/gprotein)
1	Normalcontrol	23.5±0.72	1.09±0.27	10.7±0.21	**13.58±0.28**
2	Vincristine 100µg/kg/dayi.p.	12.73±0.35***	2.06±0.35***	5.04±0.26***	**65.44±0.26*****
3	Methylcobalamin50µg/kgi.p.	19.10±0.29!!!	1.53±0.98!!!	10.07±0.34!!!	39.76±0.74!!!
4	Mormordica charantia100mg/kg,P.O.	17.15±0.67##	1.73±0.47##	12.96±0.29##	**42.62±0.68**##
5	Mormordica charantia 200mg/kg,P.O.	19.69±0.74##	1.15±0.26##	10.63±0.11##	**36.93±0.37**##

Values are expressed as Mean ± S.E.M (n=6). ***p<0.001 compared to normal control; !!!p<0.001 compared to disease control; ##p<0.01 compared to standard Methylcobalamin control.

Histopathological Studies

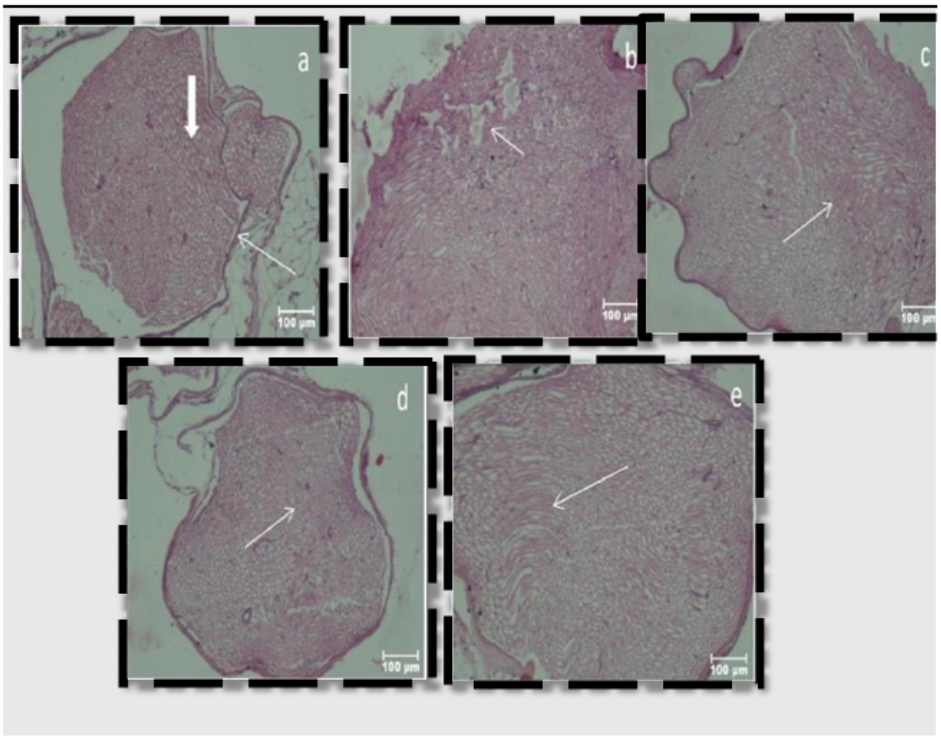

Figure 2: Histological analysis of sciatic nerve tissue.

(a) Normal control group showing intact sciatic nerve architecture with well-defined perineurium (arrow), numerous nerve fibers with centrally placed axons,

intact myelin sheath (thick arrow), endoneurium, and Schwann cells.

(b) Vincristine (100 µg/kg/day, i.p.) group showing disrupted nerve architecture, loss of perineurium, reduced nerve fibers, and fluid accumulation (arrow).

(c) Methylcobalamin (50 µg/kg, i.p.) group showing restored perineurium and nerve fibers with axons surrounded by myelin sheath and normal endoneurium and Schwann cells (arrow).

(d) Momordica charantia 100 mg/kg, P.O. group showing normal perineurium, nerve fibers with axons and myelin sheath, endoneurium, and Schwann cells with characteristic wavy appearance of fibers (arrow).

(e) Momordica charantia 200 mg/kg, P.O. group showing dense nerve fibers with intact perineurium, axons with myelin sheath, endoneurium, and Schwann cells, similar to normal control (arrow).

H&E staining. Scale bar = 100 µm.

Conclusion

Methanolic root extract of Momordica charantia effectively attenuated vincristine-induced peripheral neuropathy in rats. It improved pain behaviors, enhanced nerve conduction velocity, reduced pro-inflammatory cytokines, restored antioxidant levels, and preserved sciatic nerve architecture. These findings suggest that M. charantia exerts neuroprotective effects through antioxidant and anti-inflammatory mechanisms, highlighting its potential as a therapeutic agent for chemotherapy-induced neuropathy.

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