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Original Article

Hydroethanolic extract of *Lavandula angustifolia* ameliorates vincristine-induced peripheral neuropathy in rats

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Abstract

Background and purpose: Peripheral neuropathy is one of the most common adverse effects of cancer chemotherapy. Vincristine is prescribed to treat a variety of carcinomas, including lymphoma and leukemia, and may cause progressive peripheral neuropathy due to the damage of microtubules and mitochondria of neurons and affects inflammatory processes. This study was designed to evaluate the effects of *Lavandula angustifolia* hydroalcoholic extract (LHE) of aerial part on vincristine-induced peripheral neuropathy in a rat model.

Experimental approach: Neuropathy was induced in rats by daily intraperitoneal administration of vincristine (0.1 mg/kg for 2 weeks). Following the induction of neuropathy, animals were treated with the LHE (100, 200, and 400 mg/kg, p.o.) or pregabalin (20 mg/kg, IP) for 2 weeks, and their responses to vincristine-induced hyperalgesia and locomotor impairment were measured.

Findings/Results: LHE, at the dose of 400 mg/kg, showed analgesic effects in response to thermal hyperalgesia, tactile allodynia, and gait impairment. Also, pregabalin (20 mg/kg, IP) improved the symptoms of vincristine-induced peripheral neuropathy.

Conclusions and implications: According to the results, we can conclude that LHE alleviates neuropathic symptoms of vincristine and the effect is probably related to the presence of phenols and flavonoids in the extract.

Keywords: *Lavandula angustifolia*; Neuropathy; Vincristine.

INTRODUCTION

Chemotherapy-induced peripheral neuropathy (CIPN) is a common unwanted effect of anticancer drugs and is observed after receiving several anticancer medicines such as vinca alkaloids, taxanes, and some other chemotherapeutic drugs (1). The incidence of CIPN varies in different chemotherapeutic agents and is highly prevalent with oxaliplatin and vincristine. The rate of CIPN incidence is related to the chemotherapy duration and the symptoms are mostly observed in the first six months, like tactile hypersensitivities paresthesia, burning sensations, and feeling of numbness in the extremities. However, they might affect the quality of life of patients (2).

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Vincristine is one of the chemotherapeutic regimens to treat many types of cancer like childhood leukemia and lymphoma. Vincristine can lead to hyperpathia, hypersensitivity, paresthesia, dysesthesia, and peripheral neuropathy during treatments. The neurotoxic effect of vincristine probably is due to its antimitotic properties and it shows this effect by binding to β-tubulin and disorganizing axonal microtubule cytoskeleton (3,4). Although chemotherapeutic agent-induced neuropathy is dose-related and associated with significant changes in individual sensitivity, vincristine can induce neuropathy at regular therapeutic doses and partial or complete remission takes several months after discontinuation of the treatment (5,6).

For that reason, there is an essential need for alternative medicine to control the complication of neuropathy, especially in neuropathic injuries caused by chemotherapy. In this regard, traditional and herbal medicine could be one of the best possible solutions to this impediment.

The effects of various herbal medicines such as *Ocimum sanctum* L., *Curcuma longa* L., *Sophora flavescens* Ait, and *Salvia officinalis* in the management of induced neuropathic pain have been demonstrated in several studies (7,8,9). Since the positive effects of herbal medicines on neuropathic pain have been confirmed by some clinical studies, the discovery of new herbal remedies for neuropathic pain management seems to be essential (10,11).

Lavandula angustifolia, commonly known as lavender (syn. *Lavandula officinalis*; Lamiaceae family), is an aromatic plant native to the Mediterranean region. Analgesic, anti-inflammatory, sedative, antidepressant, anxiolytic, and dementia-preventing properties of this plant have been reported in previous research (12,13,14,15). Lavender is widely distributed in Iran and commonly known as “ostokhoddous”, and is traditionally used to treat digestive problems, cough, and inflammation (16).

In this study, according to the Iranian traditional medicine (ITM) manuscripts; lavender was selected for investigation as a treatment of neuropathy. Since the term "neuropathy" didn’t exist in medieval times and it was not exactly mentioned in ITM, we decided to find similar symptoms to this disease. A group of sensory impairment symptoms such as tingling, pain, paresthesia, and numbness, similar to neuropathy, were searched in ITM references, and all the herbal medicines used to treat these symptoms were compiled. Among the medicinal plants used to treat these complications, lavender was one of the most relevant, repeated, and emphasized ones in ITM manuscripts, which was used orally to relieve symptoms related to neuropathy. Consequently, this plant was selected as a good candidate to evaluate its effect on CIPN, and in order to extract almost whole compounds similar to traditional uses; total aerial part hydroalcoholic extract of lavender was prepared. Total hydroalcoholic extract of *Lavandula* was used to obtain a rich extract that contained most of the compounds in the plant (17). Despite previous studies, the effects of lavender on CIPN have not been investigated yet. While the definite mechanism of the vincristine-induced peripheral neuropathy development is complex and not well-known. This study was designed to investigate the effects of *Lavandula angustifolia* hydroalcoholic extract (LHE) on vincristine-induced peripheral neuropathy in a rat model.

MATERIALS AND METHODS

Plant material and extraction

Dried aerial parts of *L. angustifolia* were prepared from the local market and were identified by a qualified botanist (Voucher No. HMS557) and were deposited in the herbarium of Traditional Medicine and Materia Medica research center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. After that, they were powdered and macerated with ethanol 70% for 24 h, and this process was repeated 3 times. After each extraction, the residues were filtered and the solvents were summed up and evaporated to dryness by a rotary evaporator apparatus. The final extract was kept at 4 °C until used.

Animals

Wistar rats weighing 200-250 g were used for this study. The animals had free access to food and water and a 12/12-h light/dark cycle was maintained. The experimental protocols were approved by the Institutional Animal Ethical Committee and the experiments and care of the animals were carried out according to ethical standard instructions of the Institutional Animal Care and Use Committee (IACUC) of Shahid Beheshti University of Medical Sciences with approval code IR.SBMU.RETECH.REC.1398.054.

Drugs and chemicals

Vincristine sulfate (Sobhan. Oncology Co., Iran) and pregabalin (Sobhan Darou Co., Iran) were dissolved in normal saline (0.9% NaCl). All the extracts of *L. angustifolia* were orally administered using gavage while vincristine sulfate and pregabalin were intraperitoneally administrated to the animals. All drug solutions were prepared immediately before starting the experiments.

Experimental design

Forty-eight male Wistar rats were divided randomly into 6 groups. We ran an open field test first and then, the same animals were used for footprint test, grip strength, Von Frey, and finally hotplate test.

Group 1, control group, healthy rats with no treatments (daily administrated with 0.1 mL/kg of normal saline (i.p.); group 2, neuropathy induced group (lavender 0 mg/kg), daily administrated with 0.1 mg/kg of vincristine sulfate (i.p.) for 2 weeks; groups 3-5, treated group (lavender 100, 200, 400 mg/kg), daily administrated with 0.1 mg/kg of vincristine sulfate (i.p.) and 100, 200, 400 mg/kg of LHE, respectively, by oral gavage for 2 weeks; group 6, treated group (pregabalin 20 mg/kg), daily administrated with 0.1 mg/kg of vincristine sulfate (i.p.) and 20 mg/kg of pregabalin (i.p.) for 2 weeks.

Induction of peripheral neuropathy by vincristine

Peripheral neuropathy was induced by the administration of vincristine sulfate (0.1 mg/kg intraperitoneally once a day) for 2 weeks (18,19).

Open field test

The general locomotor activity of rats was assessed by an open field test. The rat was put inside the box constructed of plexiglass with the dimension of 60 × 60 × 60 cm. After treatment, rats were placed in the center of the box and observed for 10 min. Locomotor activity was recorded by a digital camera put above the apparatus connected to a computer. The area of the test was cleaned with 70% ethyl alcohol and left to be dried before the next test. All recorded videos were analyzed by Ethovision XT software (Noldus, The Netherlands), and the total distance moved by the animals was reported (20-22).

Hot plate test

Thermal hyperalgesia was measured by the hot plate method as described previously by Eddy *et al*. (23). We placed the rats on the hot plate (52.5 ± 0.5 °C) until animals showed the hind paw withdrawal response to the heat and the corresponding time was considered as the nociceptive threshold. The latency to show hind paw withdrawal behaviors such as licking, lifting, or jumping from the surface of the plate was reported. A cut-off time of 40 s was maintained (23).

Von Frey hair test

Mechanical allodynia was assessed by evaluating the withdrawal threshold of the hind paw response to a series of von Frey filaments. In brief, rats were placed into a plexiglass box (Borj Sanat Azma, Iran) and after 30 min of adapting to the environment, their plantar surface of the paw was stimulated with von Frey filaments (Stoelting, USA). Each test was repeated three times and the average time was calculated and expressed as an overall response (24).

Grip strength

Grip strength test was used for evaluating muscular strength after vincristine injection. To perform the test, the tails of the animals were pulled while they could grab a metal wire with their forelimb. Muscle strength was determined by the force applied to the wire by each animal.

The force used by the animals was recorded. The trial was repeated 3 times for each animal with a 5 min interval (25).

Footprint test

Footprint test was performed to assess the recovery of locomotor activity. The test was performed 14 days after injection of vincristine and oral administration of the extracts. Animals were first allowed to acclimate to their surroundings and then their hind limb was dipped in ink and they were permitted to walk on a white paper placed on the surface of the track. The areas of the footprints of rats while walking down the track on the paper were measured using Image J software (26).

Statistical analysis

All data were expressed as mean ± SEM and were analyzed by one-way ANOVA followed by post hoc Tukey's multiple comparison test. Results were described as significant at $P < 0.05$. All data were analyzed by the GraphPad Prism (v. 8) software.

RESULTS

Open field test

Locomotor activity was evaluated by the total distance the rat moved in the open field box. Different groups were treated with vincristine at the dose of 0.1 mg/kg followed by oral administration of 100, 200, and 400 mg/kg of LHE or pregabalin (20 mg/kg). As shown in Fig. 1, vincristine caused a significant decrease in motor activity (980 ± 214 cm) compared to the control group (2360 ± 181 cm). Treatment with LHE at 400 mg/kg (2017 ± 203 cm) and pregabalin (2226 ± 314 cm) could significantly reverse this disability in movement.

Hot plate test

Administration of vincristine caused a significant decrease in latency time to react to heat stimulation (hyperalgesia) (26 ± 2 s) compared to the control group (56 ± 2 s) in Fig. 2. Oral administration of LHE attenuated the vincristine-induced hyperalgesia at the dose of 400 mg/kg (48 ± 3 s). Moreover, pregabalin showed a significant effect (50 ± 4 s) in latency time to heat stimulation compared to the vincristine group.

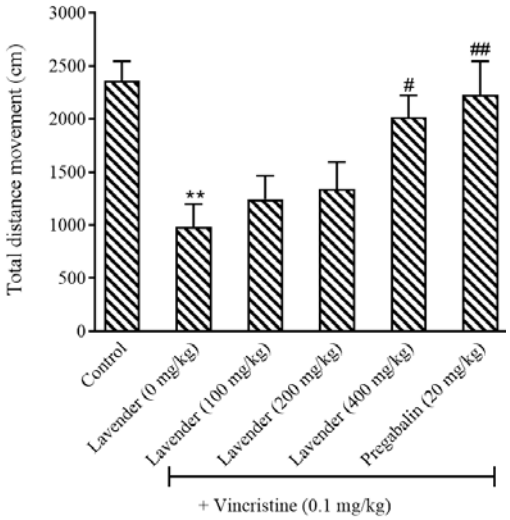

Fig. 1. Effect of *Lavandula angustifolia* (100, 200, and 400 mg/kg) on open field test in vincristine-induced neuropathic pain. Data are expressed as mean ± SEM, n = 8. $^{**}P < 0.01$ Indicate significance differences in comparison with the control group; $^{\#}P < 0.05$ and $^{\#\#}P < 0.01$ versus vincristine-treated (lavender 0 mg/kg) group.

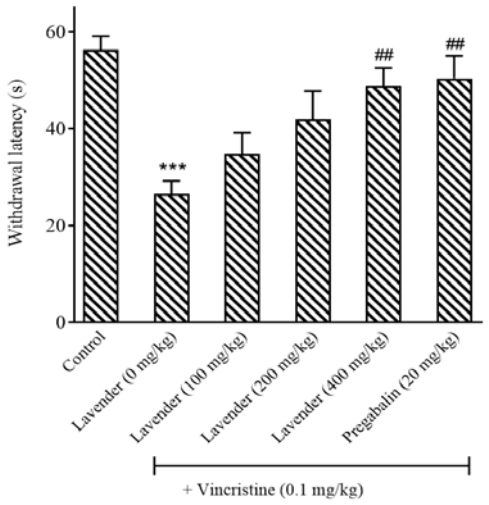

Fig. 2. Effect of *Lavandula angustifolia* (100, 200, and 400 mg/kg) on hot plate test in vincristine-induced neuropathic pain. Data are expressed as mean ± SEM, n = 8. $^{***}P < 0.001$ Indicate significance differences in comparison with the control group and $^{\#\#}P < 0.01$ versus vincristine-treated (lavender 0 mg/kg) group.

Von Frey hair test

As shown in Fig. 3, the nociceptive threshold to the mechanical von Frey filaments was significantly reduced after vincristine injection during the experiment (8 ± 1 g) compared to the control group (47 ± 6 g). On the other hand, animals treated with 400 mg/kg LHE showed a significant paw withdrawal reaction (50 ± 6 g) compared to the group that received only vincristine. However, mechanical sensitivity induced by vincristine didn't decrease in animal groups treated with LHE at 100 mg/kg or 200 mg/kg (7 ± 1 g and 27 ± 7 g, respectively).

Grip strength

In this part of the study, we evaluated the neuropathy by assessment of muscle strength using measuring grip strength test. Compared to the normal rats, the grip strength of vincristine-received animals significantly decreased (266 ± 17 N compared to 355 ± 23 N; Fig. 4). None of the doses of the extracts (100, 200, and 400 mg/kg) could reverse the muscle weakness (280 ± 14 N, 279 ± 7 N, 295 ± 9 N, respectively); whereas pregabalin, at 20 mg/kg, effectively increased the muscle strength (354 ± 27 N) compared to the vincristine-received group.

Footprint test

As shown in Fig. 5, administration of LHE (400 mg/kg) and pregabalin (20 mg/kg) increased the pressure of the foot by the measurement of pixel values (5503 ± 545 and 7462 ± 866 pixels, respectively) in comparison with the group that received vincristine (1248 ± 150 pixels), which demonstrated that LHE and pregabalin could strengthen the foot muscles.

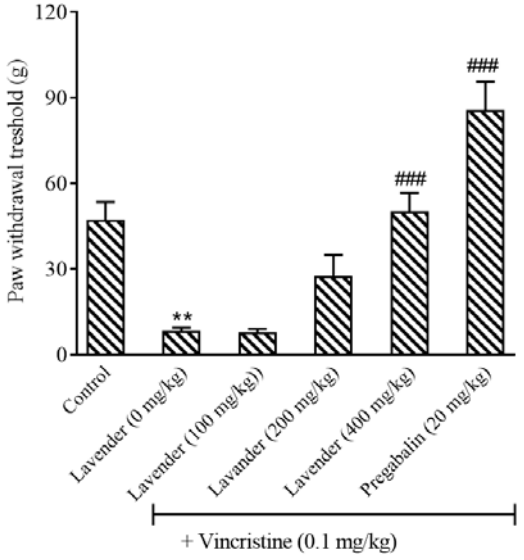

Fig. 3. Effect of *Lavandula angustifolia* (100, 200, and 400 mg/kg) on von Frey test in vincristine-induced neuropathic pain. Data are expressed as mean ± SEM, n = 8. $^{**}P < 0.01$ Indicate significance differences in comparison with the control group; $^{###}P < 0.001$ versus vincristine-treated (lavender 0 mg/kg) group.

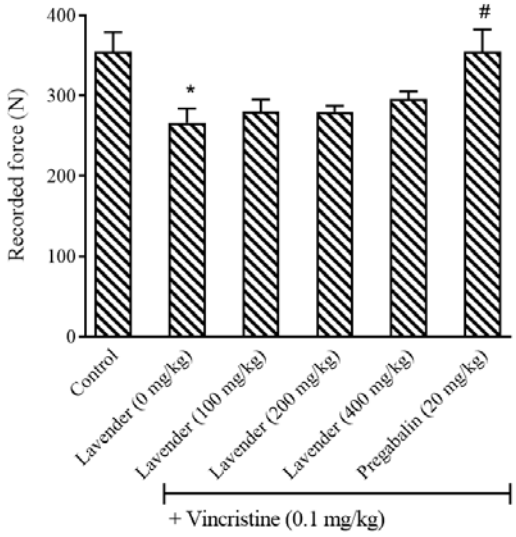

Fig. 4. Effect of *Lavandula angustifolia* (100, 200, and 400 mg/kg) on grip strength test in vincristine-induced neuropathic pain. Data are expressed as mean ± SEM, n = 8. $^{*}P < 0.05$ Indicate significance differences in comparison with the control group; $^{\#}P < 0.05$ versus vincristine-treated (lavender 0 mg/kg) group.

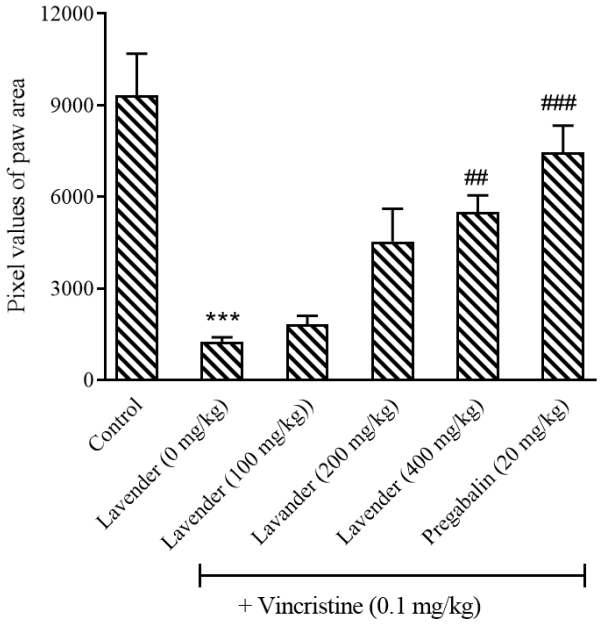

Fig. 5. Effect of *Lavandula angustifolia* (100, 200, and 400 mg/kg) on foot print test in vincristine-induced neuropathic pain. Data are expressed as mean ± SEM, n = 8. ***$P < 0.001$ Indicate significance differences in comparison with the control group; ##$P < 0.01$ and ###$P < 0.001$ versus vincristine-treated (lavender 0 mg/kg) group.

DISCUSSION

Administration of vincristine is limited due to inevitable adverse effects including CIPN. Since there is no effective prevention or treatment for CIPN, many patients have to reduce their therapeutic dose or terminate the use of vincristine (27). The effectiveness of various herbal medicines to alleviate vincristine-induced peripheral neuropathic pain has been reported in rats. Saponin-rich fraction of *Ocimum sanctum* attenuated vincristine-induced painful neuropathic state through reducing calcium levels and oxidative stress (6). In another study, it has been shown that curcumin isolated from *Curcuma longa* significantly attenuated vincristine-induced neuropathy following calcium inhibitory action and antioxidant activity (7)

In the present study, the potential protective effect of the lavender aerial part extract was evaluated in an animal model of vincristine-induced CIPN in order to find an effective therapeutic intervention for CIPN.

Administration of vincristine for 2 weeks induced neuropathy in the subjects and the neuropathy showed behavioral changes including mechanical allodynia and thermal pain perception (von Frey and hot plate tests, respectively). In 2012, Park *et al*. used a similar protocol and they found almost the same results in mechanical allodynia and heat hyperalgesia 2 weeks after vincristine injection (28). In addition, deficits in locomotor activity, muscle strength, and weight-bearing (using open field, grip strength, and footprint tests, respectively) were measurable. Wahdan *et al.* reported a significant reduction of locomotor activity in CIPN in rats (29). In a study on adolescent rats, Li *et al*. showed that vincristine-induced peripheral neuropathy could cause muscle weakness in the subjects (30). It has been shown that pregabalin alleviates CIPN in rat models (31). In this study, pregabalin at 20 mg/kg, as appositive control, could reverse the behavioral impairments in all the experiments.

The effect of oral administration of the lavender extract (100, 200, and 400 mg/kg) was evaluated in anti-nociceptive and motor function tests. Data showed that the dose of 400 mg/kg could effectively reduce hyperalgesia induced by vincristine and the extract at 400 mg/kg could reverse the decreased locomotor activity caused by vincristine. However, in the grip strength test, none of the doses were able to ameliorate the impaired muscles power.

The grip strength test is used to evaluate the muscular strength of limbs. The chemotherapeutic agents like vincristine cause neuromuscular function impairment, but the 100, 200, and 400 mg/kg doses of LHE did not cause significant changes. The pathology involved in muscular power is different from other effects like allodynia. Our observation indicated that LHE probably does not have a proper effect on the muscular pathway. The obtained data were consistent with preceding investigations on the analgesic and anti-inflammatory effects of extracts or isolated compounds of *L. angustifulia.*

Previous studies have demonstrated that hydroalcoholic extract of lavender could inhibit the second phase of formalin test in mice, and oral administration of lavender essential oil could suppress both phases. Furthermore, essential oil inhibited carrageenan-induced paw edema and decreased the number of abdominal constrictions in the acetic acid-induced writhing test (14).

Earlier investigations on lavender essential oil proved its effectiveness in the management of neuropathic pain conditions. Data indicated that lavender essential oil reduced spinal nerve ligation-induced neuropathic pain symptoms in rats and this effect might be conducted through inhibition of inducible nitric oxide synthases expression and spinal extracellular signal-regulated kinases and c-Jun N-terminal kinases phosphorylation (32).

Furthermore, inhalation of lavender essential oil could decrease mechanical hyperalgesia and chronic inflammation in neuropathic pain and this effect seems to be mediated by central and peripheral cannabinoid 2 and opioid receptors (33).

Phytochemical studies of different parts of lavender confirmed the presence of phenolic compounds, flavonoids, and anthocyanins (34). This group of compounds, especially flavonoids, has demonstrated promising effects against neuroinflammatory diseases and neuropathic pain (35). It has been revealed that quercetin and rutin ameliorate oxaliplatin-mediated mechanical allodynia (36).

Moreover, thermal hyperalgesia and mechanical allodynia induced by spinal nerve ligation were found to be reduced by the flavonoids myricetin and baicalein (37,38).

The evidences show that besides analgesic effects, flavonoids play a pivotal role in diminishing inflammation responses by inhibiting eicosanoid-producing enzymes and blocking arachidonic acid metabolism (39). Consequently, it can be concluded that flavonoids, as the major bioactive compounds in lavender extract, are potential therapeutic agents for neuropathic pain.

Therefore, as it was mentioned in ITM documents, the ability of the lavender extract to effectively modulate hyperalgesia and disturbed-locomotor function would considerably improve the general symptoms of vincristine-induced neuropathy and it could be considered as a potential treatment in further studies.

CONCLUSION

In conclusion, the results of this study demonstrated that the hydroalcoholic extract of aerial parts of *L. angustifulia* ameliorated the CIPN in the rat model. The extract had a significant effect on the reduction of hyper analgesia and locomotor activity impairment induced by vincristine. Therefore, it may offer a therapeutic approach for patients suffering from CIPN following adequate studies.

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Conflict of interest statement

The authors declared no conflict of interest in this study.

Authors' contributions

M. Khoramjouy, M. khakpash, and S.A. Askari contributed to the investigation; Sh. Sahranavard, M. Khoramjouy, and M. Faizi wrote the original draft of the manuscript; Sh. Sahranavard, M. Mosaddegh, and M. Faizi contributed to the conceptualization of the study, writing and editing the manuscript; M. Mosaddegh and M. Faizi contributed to project administration and supervision.

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