RESEARCH ARTICLE

The Assessment of Ferulic Acid in Rats with Vincristine-Induced Neuropathy

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ABSTRACT

The main goal of the current investigation was to find out how ferulic acid (FA) affected the neuropathic pain that vincristine caused in rats. Rats were given vincristine to cause painful neuropathy. To measure the mechanical dynamic allodynia, cold allodynia, degree of mechanical hyperalgesia, heat hyperalgesia, and muscle relaxant rota rod, respectively. Several pain-sensitive tests, including the von frey hair test, pinprick, hot plate, and rota rod, were carried out on various weeks (0, 4 and 8 weeks) as indicators of inflammation and oxidative stress the IL-1β, IL-10, tumour necrosis factor-alpha (TNF-α), tissue parameters like Na^+/K^+ ATPase, Ca^{2+} ATPase & Mg^{2+} ATPase and superoxide dismutase (SOD), catalase (CAT) level, reduced glutathione (GSH), lipid peroxidase (LPO), NO level were assessed. Gabapentin (30 mg/kg i.p.) in addition to FA (50, 100, as well as 150 mg/kg orally) was given for 08 weeks. FA administration markedly decreased vincristine-induced behavioral and biochemical alterations ($p < 0.05$). FA also reduced the inflammation IL-10 and increased IL-1β and TNF-α. FA also reduces oxidative stress (LPO, NO level) and increases at (GSH, SOD, CAT levels) that vincristine caused. FA can alle*via*te the painful states brought on by vincristine-induced painful neuropathy, which might also be explained by its anti-inflammatory effects and following reduction of oxidative stress.

Keywords: Vincristine neuropathy, Oxidative stress, Ferulic acid, Gabapentin, behavioral, Biochemical alteration.

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INTRODUCTION

Vincristine, an anticancer drug from the class of vinca alkaloids, has been used to treat leukemia patients.[1] Vincristine's well-known side effect, neurotoxicity, manifests as peripheral neuropathy, autonomic neuropathy, and cranial neuropathy.[2] Hyperalgesia, allodynia, and spontaneous pain are all signs of peripheral neuropathy. About 60% of patients experience vincristine-induced peripheral neuropathy.[3] Vincristine-induced neuropathy symptoms are dose-dependent and last for several months after treatment is stopped. Painful neuropathic pain is a chief problem of unwelcome interruptions in vincristine therapies and restrictions on vincristine dose escalation. Vincristine is a plant-derived preparation with anti-neoplastic goods that is utilized for treating many different malignancies, including breast cancer, leukemia, lymphomas, as well as principal brain cancer. At therapeutic doses, it causes consistent and predictable neurotoxicity in all patients.[1-3]

Neuropathic pain can remain triggered through a lesion, toxicity of drugs, or a somatosensory system ailment.[4] Neuropathic pain is assessed towards affecting 7 to 8% of the overall people in Europe, as well as around 10% of the adult population in the US, as well as its incidence, is predicted to increase by 17% to report on market and research in 2020.[5] According to Berger *et al*., 2004 the cost of health care in neuropathic pain patients was threefold higher than in matched control subjects.[6] Despite current developments in the understanding of neuropathic pain, it is still challenging and expensive to treat it pharmaceutically.[7] Peripheral neuropathy develops as a result of inflammation. Since glial cells, macrophages, and Langerhans cells have elevated levels of cytokines necessary for the evolution of neuropathic pain, IL- 1β, IL-6 and tumour necrosis factor-alpha (TNF-α) as well as nitric oxide (NO) are involved.[8]

Phytochemical ferulic acid (FA) is present in many fruits as well as vegetables, including corn bran, wheat bran, maize bran, banana, bamboo shoots, eggplant, and orange.[9] It has been demonstrated that increasing dietary polyphenol intake, including hydroxycinnamic acids, can be found in whole grains, fruits, and vegetables, can lower the risk of developing a number of diseases.[10] Consequently, a greater

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knowledge of the biological characteristics of dietary phenolic acids, especially ferulic acid, could help develop nutritional guidelines slower the chance of developing illnesses like cancer, diabetes, cardiovascular disease, and neurological problems like Alzheimer's disease.[11]

Certain countries have approved it as a food ingredient to protect lipid peroxidation.[12] FA previously protected retinal ischemia-induced optic neuropathy in an experimental study.[13] Rats with cerebral ischemia/reperfusion injuries were given ferulic acid (100 mg/kg, intravenously) to prevent oxidative stress-related apoptotic cell death by inhibiting intercellular adhesion molecule expression of mRNA.[14] According to a Chinese study, FA may also suppress the main sensory afferent that is involved in chronic constriction injury-induced neuropathic pain (CCI), which is promoted *via* the P2X3 receptor.[15]In addition, Sung *et al*. (2012) found that FA continues to reduce injury-induced middle cerebral artery occlusion, thioredoxin and peroxiredoxin 2 levels are reduced number of damaged nerve cells.[16] Nevertheless, ferulic acid prohibited the reduction in γ-enolase expression caused by MACO in nerve cells.[17] A recent study found that combining ferulic acid as well as fish oil decreased the oxidative damage brought on by 3-nitro propionic acid in addition to neurotoxicity in the rat striatum/cerebellum by lowering oxidants, malondialdehyde, hydroperoxides, NO, as well as calcium levels.[18] FA's neuroprotective properties compelled towards investigateing its character in vincristine-induced neuropathy in the periphery in rats.

MATERIALS AND METHODS

Drug and Reagents

Gabapentin was a sample of a gift from Sun Pharmaceutical Industries Ltd. Gujarat, India. A 1,1,3,3-tetramethoxypropane, FA, 5,5′-dithio, bis 2-nitro benzoic acid, and GSH were purchased from Sigma-Aldrich in Mumbai, India. Vincristine was procured from Celon Laboratories Pvt. Ltd, Telangana (Gift sample received from Manvata Clinical Research Institute, Nashik) for the current investigations. Every chemical used in the recent investigation were of analytical grade.

Experimental Animals

For the purpose of this experiment, 180–250 g wistar albino rats of both genders were used. They were purchased from Bombay Veterinary College, Parel in India. They were fed a typical laboratory pellet chow diet while being housed in a cage with free access to water. The rats were kept in a typical light-dark cycle with temperatures between 18 and 23°C and relative humidity levels between 30 and 35%. The rats were housed in plastic cages, and to maintain the cleanliness of the cages, the bedding was replaced every other day. The Institutional Animal Ethics Committee approved the experimental protocol, and the care of the animals was in accordance with the guidelines established by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment and Forest, Government of India (MGV/PC/CPCSEA/XXXVI/01/2019/21).

Experimental Protocol

The test drug sample vincristine was administered (Intraperitoneal) in disease control rats, standard marketed drug gabapentin (30 mg/kg) and test 1 to 3 rats two 5 days cycle with 2 days pause for 8 weeks. Standard drug and test 1 to 3 were administered orally once daily after induction of neuropathy for 8 weeks through oral gavage. The dose of vincristine was considered as 100 µg/kg based on the previously reported dose suitable for causing neuropathy. FA was given orally at 50, 100, and 150 mg/kg doses with dissolved pure water. We selected dosages (50, 100, and 150 mg/kg oral) of FA for the current investigation since, in numerous neuroprotective results associated with ferulic acid, the dosage series among 50 to 150 mg/kg (oral) was utilized in rat research.[16,17] The nociceptive signal thresholds were evaluated using a variety of behavioral measures. After that, the animals as a whole were slaughtered for biochemical testing.

The Institutional Animal Ethical Committee (IAEC) gave its approval before the study could begin, and it was carried out in accordance with CPCSEA regulations.

Six groups have been formed for the animals.

Group 1: Normal control
Group 2: Disease control- Vincristine
Group 3: Standard marketed Drug- Vincristine +Gabapentin
Group 4: Test1 (Vincristine +50 mg/kg ferulic acid)
Group 5: Test2 (Vincristine +100 mg/kg ferulic acid)
Group 6: Test3 (Vincristine +150 mg/kg ferulic acid)

Vincristine Stimulates Neuropathic Pain

Vincristine sulfate (100 µg/kg/day i.p.) was given to rats to cause peripheral neuropathy for 56 days (two 5-day cycles separated by 2-day breaks).[19,20] According to Bhalla *et al*. (2015) as well as Sweitzer *et al*. (2006), distinct weeks, week 0 (prior to vincristine administration), four and eight were used to quantify pain.[21,22]

Examination of the Behavior

The mechanical dynamic allodynia, cold allodynia, mechanical hyperalgesia, heat hyperalgesia, and rota rod tests were conducted every measurement week.

Mechanical allodynia (Von frey test)

Every single rat was placed in an acrylic cage with an elevated labyrinth and subjected to a test environment for at least 15 minutes. Von Frey filament was positioned towards the plantar surface of the hind paw from beneath the mesh floor. Provide enough filament force to the paw to cause a slight bending, then hold the position for a short while. The retraction of the paw is thought to be a positive response.[23] Mechanical allodynia observations were made with six consecutive applications of various Von Frey filament forces. OXXOXO was used for recording assessments, where O stood for no withdrawal response and X for withdrawing reaction. This technique for monitoring is the Dixon up-and-down technique with a 50% gm threshold determined by an equation:

$$50\%\ g\ threshold = (xf+k\delta)^{-10}/10{,}000$$

wherever is the mean difference between stimuli (in log units) (here, 0.224) and Xfis, the last Von Frey's log unit utilized.[24,25] The recurring sequence of positive/negative replies has a tabular value of k.

Cold allodynia using acetone solution

This section utilized the acetone drop method to evaluate the cold chemical thermal sensitivity. Rats were placed in a cage with a metal mesh, and they were given 20 minutes to become acclimated to it. A gentle acetone drop (50 µL) application was made over the mid-plantar area of the back paw. It causes paw linking, shaking, or rubbing of the hind paw together through a swift foot withdrawal, subsequently applying a solution of acetone, which was thought to have an anti-nociceptive action.

- *Pin prick test for mechanical hyperalgesia*

In order to induce a reflex withdrawal reaction in a normal rat, A bent 18 gauge needle was briefly in touch with the plantar surface of the left hind paw (at a 90° angle), but none of the groups were able to pierce the skin with this pressure. The duration of the paw's withdrawal was measured every two weeks in seconds.

- *Thermal hyperalgesia (Hot plate test)*

The threshold for thermal nociception was studied using Eddy's hotplate, which was kept at a temperature of 52 ± 2°C. Animals were tested individually by being placed on a hot plate and measuring their paw-licking latency (in seconds). The 20-second test cut-off period was kept.[26]

- *Rota rod test for evaluating motor impairment (Rota rod test)*

Rats were tested utilizing a rota rod apparatus while being rotated at a speed of 15 rpm. Each rat's fall-off time from the rotating spindle was timed over a five-minute period.

Estimation of Cytokines Level

According to Krishgen Biosystems' ELISA cytokine kit, which was created for the simulated flow cytometric cytokine detection at the Pune-based APT Research laboratory,

Biochemical Estimations

In the eighth week, ketamine (140 mg/kg, i.p.) was utilized as a high-dose anesthetic during all of the animal sacrifices. The sciatic nerve (from both legs) and tissue beneath them were promptly separated. Sciatic nerve tissue that was excised was located between the point of transection and the point at which it emerged since the spinal cord was terminated. The sciatic nerve transection site was precisely beneath the center of a portion of tissue that was 1-cm in diameter. The sciatic nerve segments were subsequently separated in addition to testing over SOD, CAT, GSH, LPO, and NO. The samples were afterward frozen and examined simultaneously. The 10% w/v sciatic nerve homogenate (pH 7.4) was developed using 0.1 M tris-HCl buffers. After being immersed in ice water for 30 minutes, the homogenate-containing tubes were centrifuged at 2000 rpm for 10 minutes at 4°C. Calculations for SOD, CAT, GSH, LPO, and NO were done using the homogenate supernatant, which was separated.

Assay of superoxide dismutase

In accordance with the process outlined by Kakkar *et al*. (1984), SOD was measured in the nerve homogenate. At 560 nm, superoxide anions were used to reduce NBT to blue formazan beneath aerobic situations. The degree of enzyme activity is determined by the amount of inhibition that occurs when SOD is introduced. The enzyme's activity was expressed in units/mg protein, where a unit of enzyme is defined as an amount that reduces the rate of reaction by approximately 50%.[27]

Catalase analysis

Catalaseaction was measured using the Beers and Sizer (1952) technique in the nerve homogenate. The spectrophotometric monitoring of hydrogen peroxide (H_2O_2) breakdown in CAT followed the decline in 240 nm absorbance. The enzyme's action was measured in mmoles of H_2O_2 decomposed or milligramme of protein per min.

Assessment of GSH

GPx action was assessed using Paglia and Valentine's (1967) technique in the nerve homogenate. The process gauged how quickly reduced GSH was being oxidized through H_2O_2 and initiated *via* the GPx. By including exogenous glutathione reductase and nicotinamide adenine dinucleotide phosphate (NADPH), which instantly convert whichever developed oxidized glutathione disulfide (GSSG) to GSH, GSH is kept at a consistent concentration. Then, for 5 minutes, the absorbance of NADPH at 340 nm is monitored to determine the rate of GSSG production. The action of the enzyme was measured in moles of NADPH-oxidized mM/mg protein units.

Measurement of tissue nitrite level

According to Green *et al*., 1982, the Griess reagent content 1% sulfanilamide in 5% phosphoric acid and 0.1% naphthyl ethylenediamine hydrochloric acid in water (a 1:1 ratio) was used to measure the amount of nitrate/nitrite in the nerve homogenate. At 540 nm, the color saturation of the chromogen was determined. Outcomes were given in units of mM/mg protein.[28]

Statistical Analysis

Version 5.0 of Graph pad prism was used to calculate Mean + SEM from the data, which were then subjected to a one-way ANOVA to determine their statistical significance.

RESULT

Effect of FA on Vincristine-Induced Allodynia

Now, in comparison to the control group, vincristine administration led to a considerable improvement of mechanical dynamic allodynia (Figure 1) in addition to cold allodynia (Figure 2). Vincristine that has been FA attenuated is administered, and this significantly causes allodynia ($p < 0.05$). Additionally, in mechanical dynamic allodynia, FA administered had a better effect on vincristine-induced neuropathy than when compared with standard vincristine after 8 weeks ($p < 0.05$) (Figure 1). Additionally in cold allodynia, FA administered had an increased effect on vincristine-induced

neuropathy than when compared with standard GBA after 8 weeks ($p < 0.05$) (Figure 2). When all FA attenuated results show similar results to standard GBA.

FA Effect on Vincristine-Induced Hyperalgesia

Mechanical and thermal hyperalgesia were brought on through vincristine treatment in comparison to the control group (Figures 3 and 4). FA (50, 100, and 150 mg/kg) substantially increased the beginning of hyperalgesia while reducing vincristine treatment ($p < 0.05$). Additionally, in mechanical hyperalgesia, FA administered had a better effect on vincristine-induced neuropathy than when compared with standard vincristine after 8 weeks ($p < 0.05$) (Figure 3). Additionally, in thermal hyperalgesia, FA administered had an increased effect on vincristine-induced neuropathy than when compared with standard GBA after 8 weeks ($p < 0.05$) **(**Figure 4), when all FA attenuated results show similar results to standard GBA.

Vincristine-caused Neuropathy and the Impact of Ferulic Acid on Heat Hyperalgesia

Effect of ferulic acid on motor impairment in vincristine-induced neuropathy

In contrast to the control group, vincristine administration caused an improvement of motor impairment (Figure 5). FA (150 mg/kg) attenuated vincristine administration suggestively ($p < 0.05$) enlarged the induction of motor impairment. Additionally, the administration of FA alone had a better outcome in treating vincristine-induced neuropathy (Figure 5). When compared GBA, it also show similar results as FA showed.

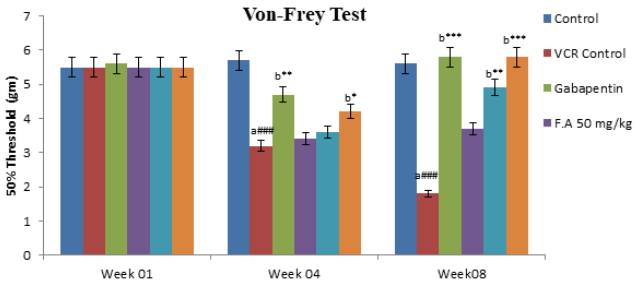

Figure 1: The effects of ferulic acid on mechanical dynamic allodynia in vincristine induced neuropathy

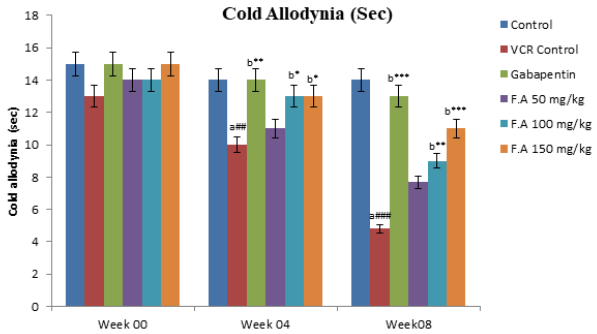

Figure 2: Vincristine-induced neuropathy, the impact of ferulic acid on cold allodynia

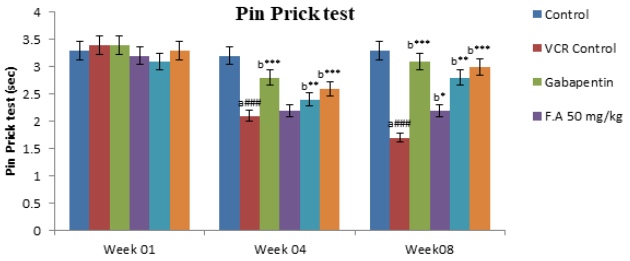

Figure 3: The impact of ferulic acid on hyperalgesia in vincristine induced neuropathy

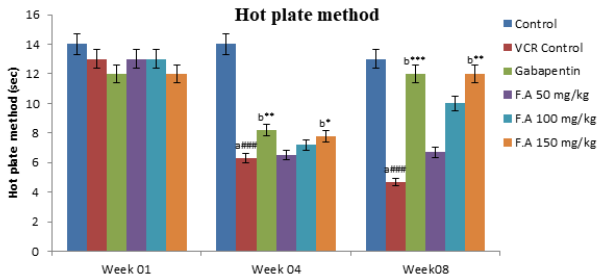

Figure 4: Vincristine-caused neuropathy and the impact of ferulic acid on heat hyperalgesia

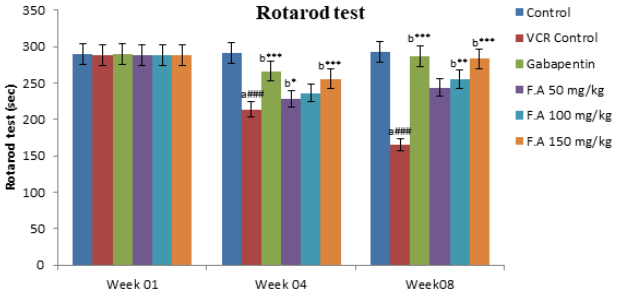

Figure 5: Vincristine-induced neuropathy and the impact of ferulic acid on motor dysfunction

Effect of ferulic acid on the amount of cytokines in vincristine-induced neuropathy

TNF-alpha and IL-1ß levels significantly increased after vincristine administration when comparing to the control. However, compared to the control, it significantly decreased the levels IL-10. Vincristine caused increases in tumour necrosis factor-alpha & IL-1ß levels were significantly (p 0.05) attenuated by FA treatments for 8 weeks. FA, however, accelerates the decline in IL-10 levels brought on by vincristine. However, as shown in (Figures 6 and 7), the administration of FA significantly alters the concentration of IL-1β, IL-10 and TNF-α in vincristine-induced neuropathic pain.

Impact of FA on tissue parameter levels in vincristine-induced neuropathy

When compared towards the control, vincristine administration significantly constant the levels of Na^+/K^+ ATPase. However, compared to the control, it significantly raised the Ca^{2+} & Mg^{2+} ATPase levels. FA administrations for eight weeks significantly ($p < 0.05$) increased the vincristine-induced Na^+/K^+ATPase levels in rats. FA does, however, increase in the

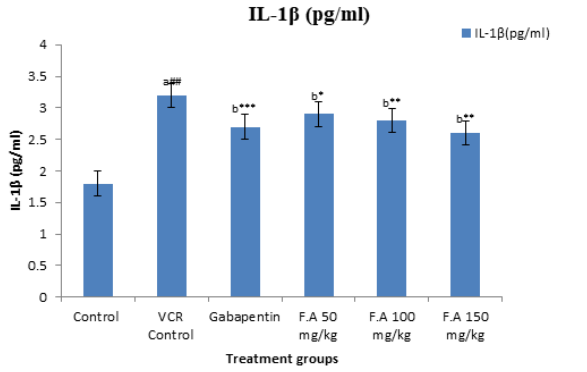

Figure 6: Vincristine-induced neuropathy and cytokines (IL-1ß)

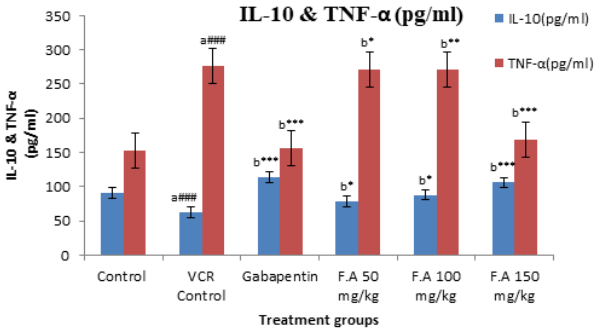

Figure 7: Cytokines (IL-10 and TNF-α) in vincristine-induced neuropathy

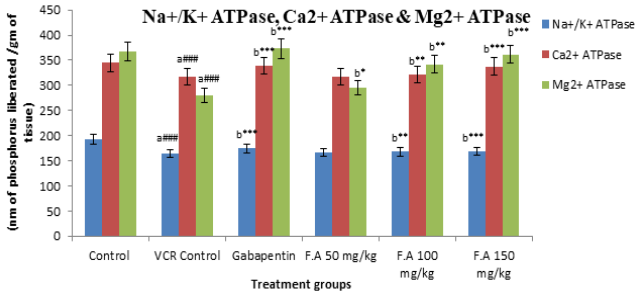

Figure 8: Tissue level parameter in vincristine-induced neuropathy

Ca^{2+} and Mg^{2+}ATPase levels brought on by vincristine. As indicated in (Figure 8), the injection of GBA significantly show the level of all ATPase as FA showed in vincristine-induced neuropathic pain.

Effect of FA on oxidative stress indicators in vincristine-induced neuropathy

When compared to the control, vincristine caused a sizable drop in GSH levels. Administration of the FA significantly ($p < 0.05$) reduced the vincristine-induced increase in the Glutathione level in the sciatic nerve. Additionally, treatment of FA compared through standard GBA had aim proved outcome ($p < 0.05$) (Figure 9 (C).

FA influence on the inflammatory marker in vincristine-induced neuropathy

Compared to the control, administering vincristine substantially improved the stages of LPO. Consuming the FA significantly reduces the vincristine-induced rise in tissue LPO ($p < 0.05$). Additionally, when FA was administered, the results were similar ($p < 0.05$) than standard GBA (Figure 9 (D). Vincristine administration considerably raised NO levels (Figure 9 (E) compared to the control. When compared towards the control, vincristine administration significantly declined the levels of SOD (Figure 9 (A). When compared towards the control, the administration of vincristine significantly raised the decline of CAT (Figure 9 (B). As indicated in all shown figures. Overall, from all inflammatory markers SOD, GSH, and CAT levels raised and NO, LPO levels declined in vincristine-induced neuropathy

DISCUSSION

The nociceptive threshold for both painful and non-painful response was significantly reduced by vincristine injection in the current investigation, indicating the development of mechanical, cold allodynia, mechanical, and thermal hyperalgesia. Following vincristine administration, these behavioral changes began in the first week and peaked in the subsequent weeks. The behavioral changes brought on by vincristine that were seen in this investigation are consistent with other observations.[29,30] Vincristine additionally caused biochemical alterations in the form of a drop in IL-10 and an upsurge in the levels of GSH, SOD, CAT, NO, TNF-alpha, IL-1β.[31]

Additionally, according to recent experiments studies, IL-10 therapy reduced CCI, sciatic inflammatory neuropathy, and mechanical allodynia brought on by intrathecal HIV-1 gp120.[32,33] Additionally, at the second and/or fourth weeks of

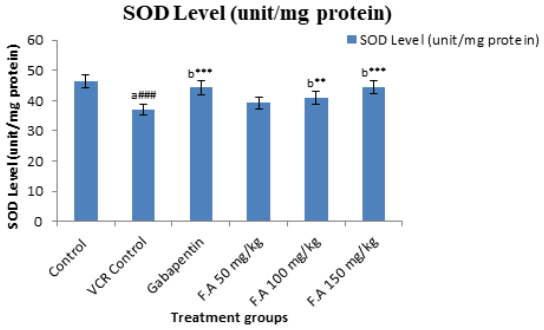

Figure 9 (A): SOD level

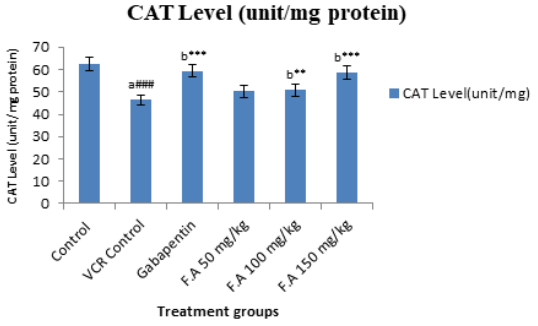

Figure 9 (B): CAT level

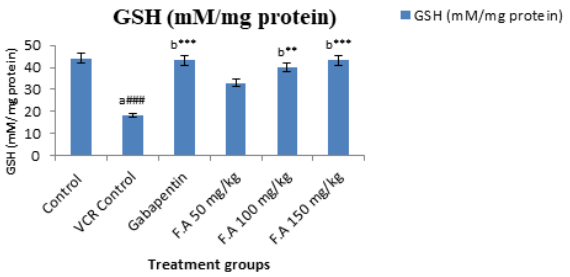

Figure 9 (C): GSH level

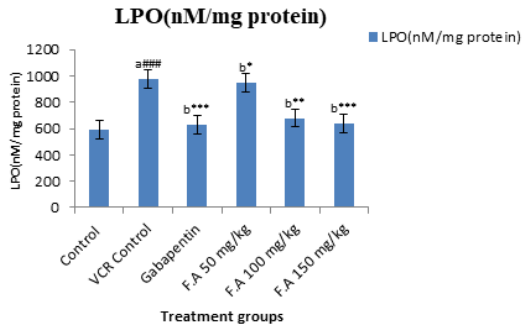

Figure 9 (D): LPO level

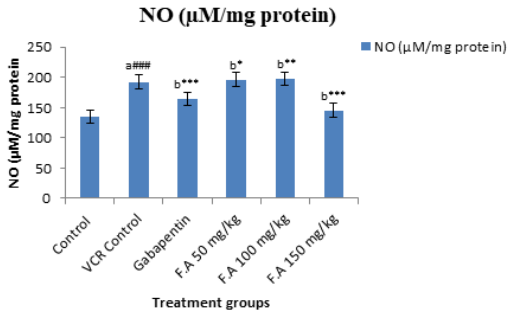

Figure 9 (E): NO level

Figure 9: Vincristine-induced neuropathy: indicators of oxidative stress and inflammation

treatment, the increased regulation of p-p38, tumor necrosis factor-α, stromal cell-derived 1-α (SDF1-α) and CXCR4 prompted through gp120 in the lumbar spinal dorsal horn and/or the dorsal root ganglion (DRG) was reversed by the expression of IL-10 through herpes simplex virus vectors[34]. It advised using IL-10 for its anti-inflammatory properties. Additionally, research using various models of spinal injury showed that IL-10 hinders the making of pro-inflammatory species like IL1 beta, IL2 and IL6, TNF-α, interferon-gamma, matrix metalloproteinase-9, NO synthase, LPO,as well as ROS.[35] IL-10 increased the anti-apoptotic proteins Bcl2 and Bcl2-linked X, B-cell lymphoma extra-large (Bcl-xl), but it down-regulated a number of causing apoptosis hesperidinctors, such as cytochrome-C, caspase-3, and Bax.[35]

FA treatment also reduced the oxidative stress brought on by vincristine. This suggests that FA-mediated oxidative stress reduction also contributes to vincristine-induced neuropathy's anti-nociceptive effect. In the current study, FA treatment decreased vincristine-induced changes in nociceptive threshold (including mechanical, thermal, and mechanical dynamic allodynia in addition to cold allodynia), pointing to its potential to be anti-nociceptive in vincristine-induced neuropathy.

TNF-alpha, IL-1ß, and LPO levels increased after the administration of FA-attenuated vincristine, indicating a decrease in neuropathy-related inflammation. The neuroprotective effects of FA in ischemia-reperfusion injury were demonstrated through (Kim and Lee 2012) to be mediated *via* lowering TNF-α, oxidative stress, in addition to JNK activation levels. The increase in oxidative stress and elevation in TNF-α and IL-1ß levels brought on by vincristine.[37]

Gabapentin (30 mg/kg i.p.) and FA (50, 100, and 150 mg/kg orally) were given for 8 weeks. FA administration significantly reduced vincristine-induced behavioral and biochemical alterations ($p < 0.05$). FA also reduced the inflammation IL-10 and increase in IL-1ß and TNF-α. FA also reduce oxidative stress (LPO, NO level) and increase at (GSH, SOD, CAT level) that vincristine caused. FA can alle*via*te the painful states brought on by vincristine-induced painful neuropathy, which also could explained by its anti-inflammatory effects and consequentdecrease of oxidative stress.

However, despite the fact that high doses of FA reduced pain, these groups still experienced significant pain. Therefore, FA high dose was used to achieve complete pain relief. Treatment with FA had a stronger anti-nociceptive effect than treatment with either drug alone. However, FA works through the mechanisms mentioned above, which encourages the use of therapy for more effective neuropathic pain relief.

CONCLUSION

Increasing of TNF-alpha, IL-1ß, levels, as well as an inhibiting in IL-10, are all indicators of FA's considerable anti-inflammatory effect, according to our study. Its antioxidant potential is supported by a decrease in NO, LPO and a rise in GSH, SOD, CAT levels caused by FA. Additionally, FA administration may be able to balance calcium homeostasis and reduce the oxidative stress and inflammation that vincristine causes. The protection of cytokine levels through ferulic acid turns out to be a crucial element in nerve regeneration, in addition to reducing electrophysiological imbalance. Furthermore, ferulic acid could develop a novel nutritional strategy for treating chemotoxic neuropathy. According to evidence, FA benefits, such as anti-inflammatory, anti-oxidative, and calcium homeostasis, in addition to a level of cytokine regulation, In vincristine-induced neuropathy caused neuroprotective action. FA eventually may prove to be cutting-edge targets for the successful treatment of painful neuropathy.

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