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Neuroprotective and Antioxidant Effects of Alpha-Lipoic Acid and Ferulic Acid Alone and In Combination Against Peripheral Neuropathic Pain Induced by Partial Sciatic Nerve Ligation in Rats

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ABSTRACT:
The goal of this preclinical study was to see how the alone and in combination drug gives their action as an antioxidant and neuroprotective effects of ferulic acid (FA) and α-lipoic acid (ALA) affects in peripheral neuropathic pain caused by partial sciatic nerve ligation (PSNL). Behavioral, biochemical, and histological assessments were conducted to validate neuropathic pain. Five groups of six adult Wistar rats were implemented. In PSNL model, to cause peripheral neuropathy partially tied on the sciatic nerve of rates under the anesthesia. After peripheral neuropathic pain induced, rats were given α-lipoic acid (25 mg/kg/day), ferulic acid (10 mg/kg/day), their combination (12 mg/kg and 5 mg/kg, respectively), or the standard treatment like gabapentin (30 mg/kg/day, i.p.) used. We assess the mechanical allodynia, mechanical hyperalgesia, cold allodynia, and thermal allodynia to find out the peripheral neuropathic pain induced to while the treatment drugs gives their effects in neuropathic pain. Biochemical tests included levels of GSH, SOD, CAT, MDA, and TNF-α. Histopathological tests were also done on sciatic nerve tissue. PSNL significantly altered the behavior and physiological indicators of rats. Therapy with α-lipoic acid and ferulic acid significantly enhanced these altered parameters, with the combination group exhibiting superior efficacy compared to individual therapies with the combination treatment drug gives the synergistic effect as comparison with the gabapentin. The enhanced anti-inflammatory, membrane-stabilizing, and free radical scavenging properties of both antioxidants gives good effects with their combination and finding the effective observed effects.

INTRODUCTION:
Neuropathic pain (NP) is a long lasting and complicated pain syndrome that happens when lesions or illnesses affect the somatosensory system in the central as well in peripheral nervous system. It causes abnormal sensory processing [1]. NP happens when nerves don't work right and feels like burning, shooting, or electric shock-like pain. In nociceptive pain the tissue is damaged or could be damaged and needs healthy neural pathways [1]. The

International Association for the Study of Pain classifies NP based on its cause, where it is located in the body, and the underlying pathophysiological mechanisms [2].

Peripheral neuropathic pain (PNP) can arise from various etiological factors, including traumatic, metabolic, viral, and drug-induced origins. Compression, strain, and transection are all types of traumatic nerve injuries that directly damage the nerve and often cause neuropathic symptoms that last for a long time [3]. Diabetes mellitus is one of the most common metabolic disorders, and about half of people with these disorders will develop diabetic neuropathy at some point in their lives. This makes it one of most common causes of peripheral neuropathy worldwide [4]. Infectious diseases like herpes zoster that damage sensory neurons can lead to post-herpetic neuralgia [5]. Chemotherapy drugs, especially platinum compounds (like cisplatin and oxaliplatin), taxanes, and vinca alkaloids, cause dose-limiting peripheral neuropathy by making axons break down and mitochondria stop working [5]. In the end, these factors keep chronic pain going by causing neuroinflammation, maladaptive neural remodeling, prolonged hyperexcitability, and decreased axonal transport [3].

Many experimental animal models have been developed to evaluate potential treatments and enhance the understanding of the mechanisms underlying neuropathic pain. Partial Sciatic Nerve Ligation model, first introduced by Seltzer et al., is widely recognized for its ability to faithfully reproduce the clinical features of neuropathic pain [6]. This model causes localized nerve damage by partially tying off the sciatic nerve, which usually affects one-third to one-half of the nerve bundle [6]. Such an injury causes Wallerian degeneration, demyelination, inflammatory cell infiltration, and an increase in over production of pro-inflammatory cytokines [7]. Because of this, this paradigm is optimal for pharmacological research due to animals exhibiting traits of NP, including mechanical allodynia and thermal hyperalgesia [6,7].

Oxidative stress, a major cause of neuropathic pain, happens when there is an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense system [8]. In brain tissues, the overproduction of ROS, including superoxide radicals, hydroxyl radicals, and hydrogen peroxide, induces oxidative damage to lipids, nucleic acids, and proteins [9]. This oxidative burden enhances the synthesis of inflammatory mediators, such as tumor necrosis factor-alpha (TNF-α) and inducible nitric oxide synthase (iNOS), through this activation of redox-sensitive transcription factors are NF-κB [10]. Oxidative stress also makes neuropathic pain worse by damaging mitochondria, killing neurons, and causing long-lasting neuroinflammation [9]. As a result, targeting oxidative stress emerged as feasible therapeutic strategy for management of PNP [11].

Antioxidants are necessary to neutralize the free radicals, restore redox balance, and the protect brain tissues from oxidative damage. Antioxidant therapies have been shown to diminish pain behaviors, regulate inflammatory responses, and preserve nerve function in animal models of neuropathic pain [11]. Alpha-Lipoic Acid (ALA) is one of these that has gotten a lot of attention because it is a strong anti-inflammatory and antioxidant. An organosulfur molecule, ALA is a cofactor for groups of mitochondrial enzymes that help with oxidative metabolism [12]. Because it is amphipathic, it can work in both lipid and water environments. ALA boosts the activity of mitochondria, removes reactive oxygen species (ROS), and replenishes the body's own antioxidants like vitamin C, E, and glutathione [13]. Also, it diminishes pro-inflammatory cytokine synthesis and safeguards neuronal integrity in neuropathic conditions by regulating redox-sensitive signaling pathways, including NF-κB and MAPK [14]. Clinical data demonstrating its efficacy in alleviating symptoms associated with diabetic neuropathy pain its translational potential [15].

Ferulic Acid (FA), a phenolic compound commonly found in plant-derived foods such as rice bran, oats, and coffee, represents another potential natural antioxidant [16]. FA exhibits significant properties of antioxidant by the scavenging ROS and reactive nitrogen species (RNS), inhibiting to lipid peroxidation, and enhancing the endogenous antioxidant defenses, including enzymes like as glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) [17]. FA not only has antioxidant properties, but it also lowers inflammation by stopping the activation of NF-κB in peripheral nerve tissues and lowering the levels of the pro-inflammatory cytokines like the TNF-α and interleukin-1β (IL-1β) [18].

Drugs and Experimental Animals:
We got gabapentin for free from MS University in Baroda, India, and we got α-lipoic acid (ALA) from Sigma-Aldrich in the US and ferulic acid (FA) from Otto-Kemi in India. All additional chemicals, reagents employed in the experiment were analytical grade and obtained from reputable, licensed suppliers [19].

The experimental study used male Wistar rats that weighed between 200 and 250 grams and were bought from the Disease-Free Animal House of Lacshmi Biofarms. The animals lived in controlled laboratory conditions with a temperature of about 22°C, a the 12-hour light-dark cycle, and a standard balanced meal from VRK Nutritional Solutions in Sangli, India. The Institutional Animal Ethics Committee of Scitesla Private Limited gave the study its approval (Approval No. SCI/IAEC/2024-25/142). All animal care and handling procedures followed the rules. For delivery, ALA, FA, and gabapentin were each dissolved in normal saline (NS) separately, and each formulation was made fresh before the dose [19,20].

Using the Partial Sciatic Nerve Ligation (PSL) Surgical Model to Cause Peripheral Neuropathy:
Seltzer et al. [6] first described the Partial Sciatic Nerve Ligation method, which was used to cause peripheral neuropathy. We put adult male Wistar rats to sleep by giving them an intraperitoneal injection of the 80 mg/kg of ketamine and 10 mg/kg of xylazine. After the right anesthetic was given, the area where the surgery would take place on the outside of the left thigh was shaved and cleaned in a sterile space. Then, a small cut was made to show the sciatic nerve by carefully pulling apart the muscle tissue around it. Then, a 9-0 silk suture was used to tie up about a third to a half of the sciatic nerve, making sure it stayed whole. This partial ligation hurts nerves in a way that is very similar to the symptoms of human neuropathic pain. After the treatment, the muscles and skin were carefully sewn back together. The animals were then given time to rest and eat and drink as much as they wanted. The post-surgery assessment examined behavioral indicators such as allodynia and hyperalgesia to confirm the successful initiation of neuropathic pain [7,21].

Protocol:
This research employed the random assignment of animals into five experimental groups, each comprising six rats, to evaluate the effects of different therapies on peripheral neuropathic pain. The disease control group was the untreated baseline. They got oral normal saline for two weeks to see how neuropathic pain naturally changes after a nerve injury. The conventional treatment group was given Gabapentin I.P. dose of 30 mg/kg (once a day) for two weeks. This is a well-known way to relieve neuropathic pain. To investigate the neuroprotective efficacy of antioxidants, the ALA-treated group received Alpha-Lipoic Acid orally at a dosage of 25 mg/kg/day for two weeks, while the FA-treated group was administered FA orally at a dosage of 10 mg/kg/day for the same duration. A group that got both FA (5 mg/kg) and ALA (12 mg/kg) orally gives once a day for two weeks was used to see if the two drugs could work together to help with neuropathic pain. During the treatment period, behavioral traits like hyperalgesia and allodynia were carefully measured using well-known pain assessment methods to see how well the treatments worked. To reduce stress on the animals and make sure that the experimental conditions were the same every time, all of the behavioral studies were done between 8:00 a.m. and 3:00 p.m.

Table no. 1. Animal Groups after confirmation of PNP.

Grouping of Animals	Animals per group	Treatment of Drugs	Drug route	Drug dosing (mg/kg)	Drug treatment duration
Group 1: Disease Control	6	Normal Saline	P.O.	-	14 Days
Group 2: Gabapentin Standard	6	Gabapentin	I.P.	30	14 Days
Group 3: ALA with CCI	6	ALA	P.O.	25	14 Days
Group 4: FA with CCI	6	FA	P.O.	10	14 Days
Group 5: FA, ALA with CCI	6	FA + ALA	P.O.	5 + 12	14 Days

Von Frey Hair Test for Mechanical Allodynia:
The up-down method from Chaplan et al. was used to test mechanical allodynia with calibrated von Frey filaments. To lessen stress and exploratory behavior, each rat was acclimatized for 15–20 minutes in a transparent acrylic container with a wire mesh base.

Standardized nylon monofilaments (von Frey hairs) were put on the nerve-damaged side of the hind paw so that they were at right angles to the plantar surface. To keep the stimulation going, each filament was bent slightly and held for 1 to 2 seconds. Quickly pulling back a paw, licking, or flinching were all positive withdrawal responses. Dixon's up-down method figured out the order in which to apply the filament, which let the 50% paw withdrawal threshold be used as a measure of mechanical sensitivity [22].

Test for Acetone Cold Allodynia:
The acetone drop method developed by Choi et al. was used to test cold allodynia. They put the animals in clear

acrylic chambers with wire mesh bases for 15 to 20 minutes before the test to keep their behavior stable. A blunt-ended syringe was used to gently inject 50 microliters of acetone into the middle of the hind paw's plantar area. The syringe did not touch the skin directly. They did this three times, with five minutes between each time. We watched the animals for 20 seconds after each treatment to see how they reacted to pain. For example, they pulled their paws back, licked, and shook. These behavioral responses worsened with cold allodynia, indicating heightened sensitivity to cold [23].

Pinprick Test for Mechanical Hyperalgesia:
The pinprick method developed by Tal and Bennett was utilized to evaluate mechanical hyperalgesia. To minimize stress-induced interference, each rat was placed in a transparent acrylic container on an elevated wire mesh platform for minimum of 20 minutes prior to the testing. Then, a sterile 22-gauge needle or a similar pointed tool was carefully placed across the middle of the hind paw's plantar area to avoid breaking the skin during stimulation. The stimulus was administered five times, ensuring a minimum interval of five minutes between applications to prevent sensitization or tissue damage. Promptly retracting the stimulated paw, vocalizing, or licking it constituted favorable nociceptive responses. To safeguard animals, a maximum cut-off duration of 20 seconds was established, and hyperalgesia was characterized as a response occurring within 1 second. To measure mechanical hyperalgesia, researchers counted the number of positive reactions out of five stimulations for each animal [24].

Thermal Allodynia Evaluated via Eddy's Hot Plate Technique:
The hot plate method that Eddy and Leimbach came up with in 1953 is often used to test how mice respond to heat. We put the rats on a hot plate at 52 ± 0.5°C and used a stopwatch to record how long it took for them to show the first nociceptive reaction, like licking their paws, pulling their hind paws away, or jumping. We checked responses after one second to make sure they were accurate and didn't include any non-specific movements. Animals that didn't react after 20 seconds were quickly taken out to avoid hurting their tissues, and the latency was noted as 20 seconds. We tested each animal three times, with a ten-minute break in between each test. Then we figured out the average withdrawal delay. A shorter delay time meant that thermal allodynia was present because it made people more sensitive to heat [25].

Oxidative stress assessment of endogenous antioxidant defense:
Tissue Homogeneous:
At the end of the study, every rat's sciatic nerve was carefully taken out and put right to away into ice-cold Tris-HCl buffer with a pH of 7.4. The separated nerve tissue was carefully cut into very small pieces with a scalpel blade. Then, to keep its shape, it was quickly put into a cooled 0.25 M sucrose solution. After that, the tissue was mixed together in a Tris HCl buffer (10% w/v, 10 mM, pH 7.4) to make a uniform mixture. We kept the homogenate on ice so it wouldn't go bad, and then we spun it at ten thausand rpm for fiftheen minutes at 0°C.

After completion of centrifugation, the clear supernatant layer was carefully taken out and used to measure a number of biochemical parameters, such as oxidative stress markers and cytokine levels, following standard procedures [26,27]. Some samples showed signs of turbidity, even though the analytical results were the same.

Evaluation of Glutathione (GSH):
We used the spectrophotometric method described by Moron to measure the amount of reduced GSH in tissue homogenates. Method depends on reaction between GSH free sulfhydryl groups and 5,5′-dithiobis-(2-nitrobenzoic acid), which makes a yellow chromogen that can be measured at 412 nm. To make the sample, an equal amount of 20% trichloroacetic acid was added to supernatant to help the proteins settle out.

The mixture was then spun in a centrifuge, and the clear supernatant that came out was collected for more research. Then, supernatant (0.25 ml) was mixed with 2.0 mL of 5,5′-dithiobis-(2-nitrobenzoic acid) reagent. A UV-Visible spectrophotometer measured the absorbance of the color that came out at 412 nm. We measured the GSH level in micrograms per milligram of protein [28].

Evaluation of Superoxide Dismutase (SOD):
SOD is an important enzyme in the antioxident that protects cells from the oxidative stress by turning superoxide radicals into the less reactive forms, such as hydrogen peroxide and molecular oxygen. We used the method described by Misra and Fridovich to find measure the activity of SOD in tissue samples. This method relies on stopping the auto-oxidation of epinephrine. First, the tissue homogenate was mixed with an equal amount of

distilled water. Next, ice-cold ethanol (0.25 mL) and then chloroform (0.15 mL) were added to solution. A cyclo-mixer mixed the solution for 5 minutes, and then it was centrifuged at the 2500 rpm for 10 minutes to get clear supernatant. Next, supernatant (0.5 mL) was taken out and mixed with carbonate buffer (1.5 mL) and EDTA solution (0.5 mL). Adding 0.4 mL of epinephrine started the enzymatic reaction, and absorbance was measured at 480 nm. After that, the SOD activity measured and expressed in units per mg of protein [29].

Evaluation of catalase (CAT):
We used the spectrophotometric method that Aebi [30] talks about, which is based on how quickly hydrogen peroxide (H2O2) breaks down, to see how active catalase (CAT) was in sciatic nerve tissue. We mixed 1 mL of tissue supernatant with phosphate buffer (1 mL, 50 mmol/L, pH 7.0) to get ready for the test. To start the enzymatic reaction, 1 mL of H2O2 (30 mmol/L) was added to 2 mL of the mixture that had already been made. We watched how catalase broke down hydrogen peroxide by watching how the absorbance at 240 nm slowly went down over a set amount of time. This decrease in absorbance means that the enzyme is acting as a catalyst. We found out how much catalase activity there was by measuring how quickly H2O2 broke down and expressing it in terms of the amount of hydrogen peroxide that was destroyed per milligram of protein per minute [31].

Evaluation of Lipid Peroxidation Malondialdehyde (MDA):
We used Slater and Sawyer's thiobarbituric acid reactive substances method to find out how much MDA, a sign of the lipid peroxidation, was in tissue samples. 2 ml of tissue supernatant were mixed with the same amount of 10% (w/v) trichloroacetic acid (TCA) to make proteins for the experiment. After 15 minutes in an ice bath, the mixture was spun in a centrifuge to make a clear supernatant. After that, the supernatant that had been recovered was mixed with thiobarbituric acid solution (2 mL) that had just been made. To help make a pink-colored MDA-TBA complex, the reaction mixture was heated a boiling the water bath for ten minutes and then quickly transfer to cooled on ice for five minutes. We used a spectrophotometer and a reagent blank as a reference to find the chromogen's absorbance at 532 nm. To find the MDA concentration, a standard calibration curve made with known MDA values was used. The results were given as nanomoles per milligram of protein [27].

Inflammatory markers assessment: Tumor Necrosis Factor-α (TNF-α):
We used enzyme-linked immunosorbent assay kit to find out how much TNF-α was in sciatic nerve tissue. We followed the steps explain by Muthuraman et al. This method has based on the specific binding of TNF-α in the sample to an anti-TNF-α antibody that is on the assay plate. A standard calibration curve was made using recombinant TNF-α levels between 0 and 20,000 pg/mL.

A microplate reader used to check the color intensity at 450 nm after the tissue homogenates had been treated according to the manufacturer's instructions. Using the standard curve, the TNF-α levels in each sample were found and reported as picograms per milligram of total protein [32].

Histopathology of the Sciatic Nerve:
After the animals were anesthetize and sacrifices at the end, both the sciatic tissues were carefully taken for histological examination. To keep their shape and stop them from falling apart on their own, the separated tissues were put in 10% neutral buffered formalin right away [33]. After fixation, the tissues went through normal histological steps, were stored in paraffin wax, and were cut into thin slices for microscopic study. Using a microtome, we cut pieces that were about 5 µm thick and put them on sterile glass slides [34]. We used hematoxylin and eosin (H&E) to color the slices so we could see the cells and axons. After staining, the slides were looked at under a light microscope to look for changes in the histology, like endoneurial edema, axonal degeneration, demyelination, and inflammatory cells [33, 34].

Statistical Analysis:
The experimental data were presented as mean ± SD for each group (n = 6). Two-way ANOVA and Bonferroni post hoc test for multiple comparisons were used to look at the statistics. Statistical significance was established by *P < 0.5.

Von Frey Filament-Induced Mechanical Allodynia:
The von Frey filament test was used to check for mechanical allodynia on Days 0, 15, and 29. In the disease control group, mechanical allodynia was validated by a significant reduction in paw withdrawal latency (PWL) on Day the 15 (5.17 ± 0.75 sec) and the Day 29 (4.83 ± 0.75 sec) in comparison to the baseline measurement on Day 0 (12.50 ± 1.05 sec) (###p < 0.001 vs. Day 0). By Day 29, gabapentin administration significantly elevated

PWL to 9.00 ± 0.89 seconds, indicating a reduction in mechanical hypersensitivity (***p < 0.001 compared to group I: disease control Day 15). Likewise, α-lipoic acid (ALA) therapy led to a notable increase in latency (9.50 ± 1.05 sec), suggesting a protective effect against pain induced by nerve injury (***p < 0.001). Ferulic acid (FA) treatment also made PWL much better, raising it to 8.67 ± 0.82 seconds on Day 29 (***p < 0.001). The moderate increase in latency (9.17 ± 1.04 sec) resulting from the combined administration of ALA and FA on Day 15 did not achieve statistical significance when compared to disease control.

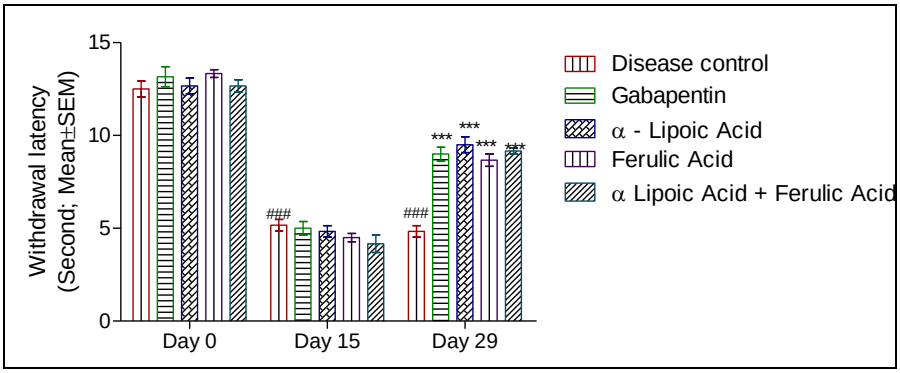

Figure 1: The von Frey filament test was used on Days 0, Day 15, and Day 29 to check for mechanical allodynia by measuring withdrawal latency time (WLT) after mechanical stimulation. The results are presented as mean ± SD (n = 6). *p < 0.05, **p < 0.01, and ***p < 0.001 show that the results are statistically significant when compared to the disease control group. ###p < 0.001 shows that the results are statistically significant when compared to Day 0.

Cold Allodynia by Acetone Test:

The acetone drop test was utilized to assess withdrawal latency time on days 0, 15, and 29, facilitating the evaluation of the effects of various therapies on cold allodynia. The disease control group had a significant decrease in withdrawal latency time on day 15 (23.00 ± 6.32 sec) and a further notable decline on day 29 (8.67 ± 2.07 sec) compared to baseline (45.00 ± 6.26 sec, ###P<0.001). This suggests that the sciatic nerve ligation made the body more sensitive to cold stimuli. Gabapentin treatment (30 mg/kg, i.p.) on day 29 made withdrawal latency much better (43.50 ± 6.06 sec, ***P<0.001), almost back to baseline levels. Rats given ALA (25 mg/kg, p.o.) and FA (10 mg/kg, p.o.) also had a big drop in withdrawal latency on day 29 (25.50 ± 4.51 sec and 23.83 ± 6.27 sec, respectively; ***P<0.001), but not as much as that given gabapentin. The oral combination of αALA (12 mg/kg) and FA (5 mg/kg) worked better than either compound alone on day 29, with a withdrawal latency time of 35.00 ± 5.44 sec (***P<0.001 vs disease control). This suggests that the two compounds may work together to reduce cold allodynia.

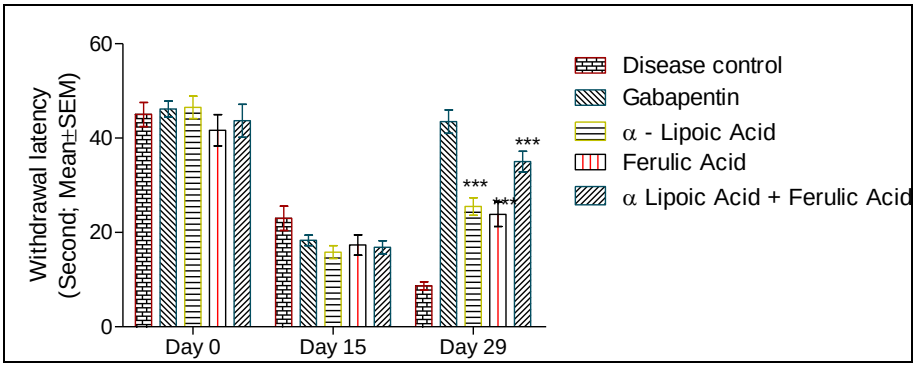

Figure 2: We measured withdrawal latency time (WLT) in response to cold stimulation using the acetone drop test on Days 0, 15, and 29 to see if someone had cold allodynia. Mean ± SEM (n = 6) is the format for the data. The disease control group had a statistically significant difference with *p < 0.05, **p < 0.01, and ***p < 0.001, and Day 0 had a statistically significant difference with ###p < 0.001. The group I: disease control exhibited a significant reduction in WLT on Days 15 and 29 relative to Day 0 (###p < 0.001), indicating the induction of cold allodynia.

Pinprick Test for Mechanical Hyperalgesia: Effect of ALA and FA:

We used the pinprick method to find out how sensitive the body was to touch, and we recorded the times it took for people to pull away on Days 0, 15, and 29. On the Day 15 (5.87 ± 1.61 sec) and the Day 29 (6.62 ± 1.42 sec), the disease control showed a significant decrease the withdrawal latency compared to Day 0 (10.53 ± 0.78 sec) (##P < 0.001). This means that mechanical allodynia successfully developed after the sciatic nerve was ligated.

Gabapentin treatment significantly increased withdrawal latency on Day 29 (10.78 ± 0.73 sec; ***P < 0.001), showing that it was effective at reducing mechanical hypersensitivity. Giving α-lipoic acid caused a small rise in latency on Day 29 (7.83 ± 1.56 sec), but this change was not statistically significant. Ferulic acid (10 mg/kg, p.o.), however, significantly increased withdrawal latency (9.28 ± 0.50 sec; **P < 0.01), showing a strong anti-allodynic effect. The combination of ALA and FA group (12 mg/kg + 5 mg/kg, p.o.) made a big difference. On Day 29, withdrawal latency dropped to 10.52 ± 0.54 sec, which was close to baseline levels (***P < 0.001).

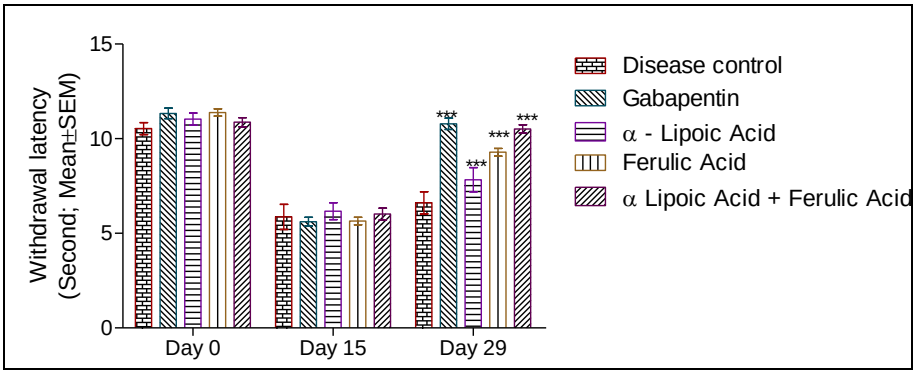

Figure 3: shows the withdrawal latency time (WLT) for the pinprick test on Days 0, 15, and 29. This test looked at mechanical allodynia in rats with sciatic nerve injuries. Mean ± SEM (n = 6) is how the results are shown, and they were looked at using ANOVA (two-way) and the Bonferroni post hoc test. *p < 0.05, **p < 0.01, and ***p < 0.001 compared to the disease control group show statistical significance. ###p < 0.001 compared to Day 0 also show statistical significance. On Days 15 and 29, the disease control group had a big drop in WLT (###p < 0.001), which means they had mechanical allodynia.

Eddy's Hot Plate Method for Thermal Allodynia:

The disease control group had a much lower withdrawal latency time (WLT) on the Day 15 (5.83 ± 1.17 sec) and the Day 29 (4.82 ± 1.17 sec) than on Day 0 (14.62 ± 0.52 sec) (###p < 0.001). This shows that thermal allodynia started after the sciatic nerve was damaged. Gabapentin treatment significantly enhanced WLT to 9.67 ± 1.63 seconds on Day 29 (***p < 0.001), demonstrating its effectiveness in alleviating thermal hyperalgesia. On Day 29, the administration of α-lipoic acid (ALA) led to a modest elevation in WLT (7.00 ± 1.10 sec; *p < 0.05), indicating a potential neuroprotective effect. Ferulic acid (FA) therapy significantly elevated WLT to 9.00 ± 0.89 sec (***p < 0.001), demonstrating strong anti-allodynic effects. On Day 29, the combination of the ALA and FA led to the biggest change in WLT (11.33 ± 1.28 sec; ***p < 0.001). This shows that the two drugs worked together to reverse thermal hypersensitivity.

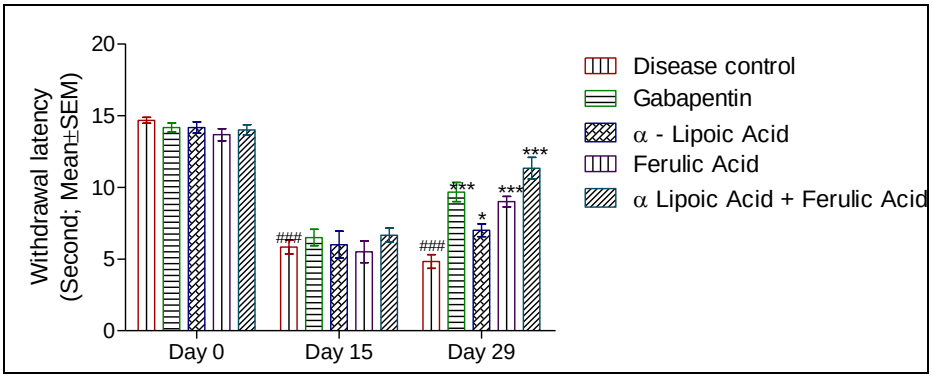

Figure 4: On Days 0, 15, and 29, rats were tested to see how long it took for them to react to thermal stimuli. The results are shown as mean ± SD (n = 6). *p < 0.05, ***p < 0.001 compared to disease control Day 15, and ###p < 0.001 compared to Day 0.

ALA and FA's Impact on Oxidative Stress (Endogenous Antioxidant Defense):

The investigation looked at SOD, CAT, GSH, and MDA as signs of oxidative stress. The disease control group had lower levels of the SOD, CAT, and GSH and higher levels of the MDA (10.63 ± 2.05 nmol/mg protein) because of nerve damage, which made the antioxidant enzyme activity go down. Gabapentin administration resulted in marginal enhancements of antioxidant parameters, evidenced by slight increases in SOD (2.65 ± 0.42), GSH (11.70 ± 1.69), and MDA (9.15 ± 0.91), yet these changes were not statistically significant when the

compared to the group disease control. The treatment with α-lipoic acid significantly improved antioxidant status, as evidenced by elevated SOD levels (3.27 ± 0.38) and a slight reduction in MDA (9.13 ± 1.03). Ferulic acid therapy made antioxidant defenses stronger by raising levels of SOD (3.08 ± 0.45) and CAT (41.55 ± 2.57) and lowering lipid peroxidation. The combination of ALA and FA had the most effect on all of the treatment groups. The highest levels of SOD (3.33 ± 0.29) and CAT (44.47 ± 5.10) were found, and GSH levels were higher (11.62 ± 0.99). MDA levels were significantly diminished (5.93 ± 2.25), signifying decreased oxidative damage and lipid peroxidation.

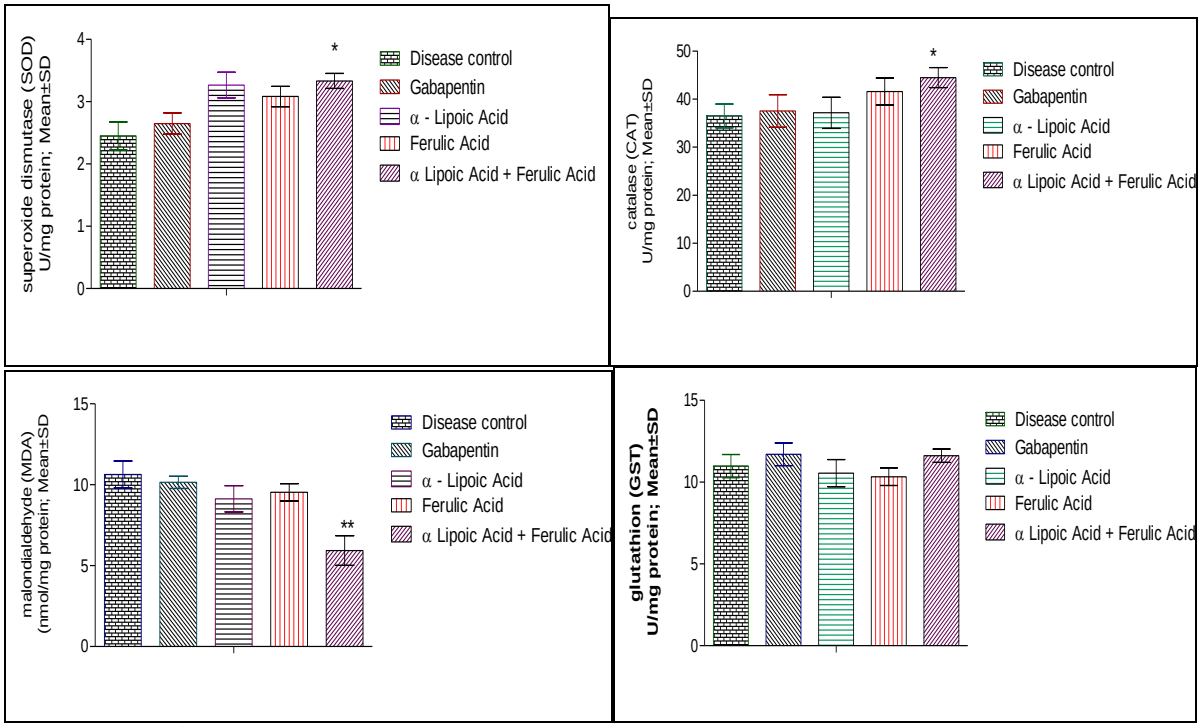

Figure 5: Impact of Antioxidant markers SOD, CAT, MDA, and GSH in Wistar rats with sciatic nerve injury. **P < 0.01 and *P < 0.05 compared to the disease control show that something is statistically significant.

Sciatic Nerve Inflammatory Marker:

The disease control group had a lot more TNF-α, an important pro-inflammatory cytokine (65.15 ± 0.26 pg/mg protein). This suggests that there was inflammation after the sciatic nerve was damaged. The fact that TNF-α dropped to 29.48 ± 0.17 pg/mg protein ($p < 0.001$ vs. group I: disease control) shows that gabapentin is a very strong anti-inflammatory drug. Also, treatment with α-lipoic acid showed some anti-inflammatory effects by lowering TNF-α levels to 39.92 ± 0.32 pg/mg protein ($p < 0.001$ vs. group I: disease control). After treatment with ferulic acid, TNF-α levels dropped a lot (29.24 ± 0.18 pg/mg protein), which was the same as what gabapentin did ($p < 0.001$). Interestingly, TNF-α levels dropped the most when α-lipoic acid and ferulic acid were given together (26.98 ± 0.42 pg/mg protein). This suggests that the two antioxidants worked together to have the strongest anti-inflammatory effect (**$p < 0.001$).

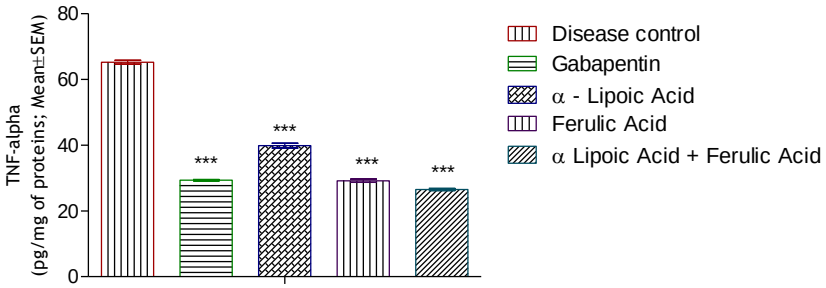

Figure 6: ALA and FA on the inflammatory marker TNF-α in Wistar rats with sciatic nerve injury. When compared to the group I:

disease control, **P < 0.01 and *P < 0.05 show that the results are statistically significant.

Histopathology of the Sciatic Nerve:

A histopathological study of the sciatic nerve was done to look at how the structure changed after peripheral nerve damage and the treatments that followed. There was a small amount of inflammatory cells in the disease control group, which meant that the axons were damaged and the brain was still inflamed. The group that got gabapentin, showed normal nerve architecture again, which means that the myelin sheath was intact, the axonal filaments were well-defined, and the nerve thickness was kept. The histological features of animals treated with α-lipoic acid showed that it was very effective at protecting the brain, and they were similar to those of the usual treatment group. Some of these features were intact myelin and axonal structures that were easy to see. The ferulic acid-treated group also kept their normal nerve structure, with intact axons and myelin, which suggests that they were protected from degenerative changes and demyelination. The combination of α-lipoic acid and ferulic acid showed a lot of nerve tissue preservation, with distinct myelin sheaths and prominent axonal filaments. This was very close to what the gabapentin group showed. These results suggest that ALA and FA work together to lessen the damage to tissues caused by peripheral nerve injury.

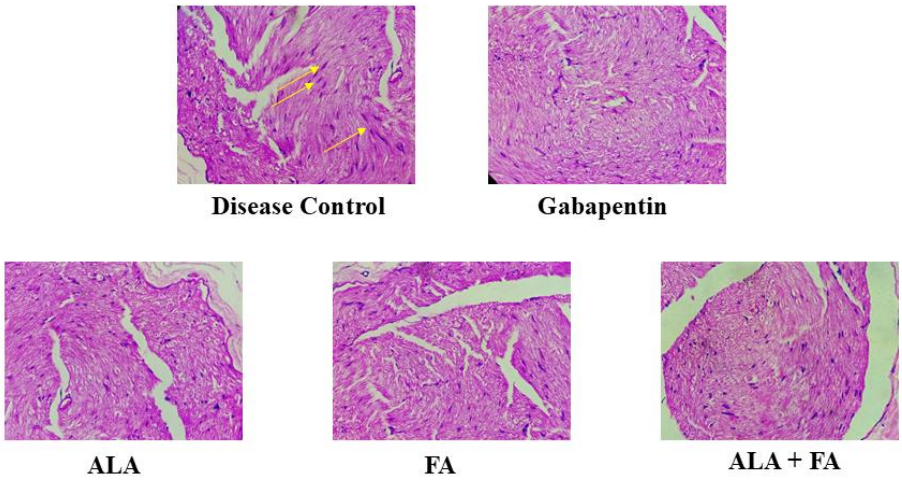

Figure 5: Histopathology seen the sciatic nerve in different groups after completion of studies induced by PSNL Model.

DISCUSSION:

When peripheral nerves are injured or not working properly, they can cause strange sensory reactions like mechanical allodynia, cold and thermal allodynia, and mechanical hyperalgesia. Peripheral neuropathic pain (PNP) is a long-lasting and debilitating condition. These disruptions are caused by maladaptive changes in central nervous systems and peripheral nervous systems, such as nociceptive pathway sensitization, glial cell activation, elevated oxidative stress, and neuroinflammatory processes [1, 3]. The PSNL model is a well-known experimental model that closely mimics the clinical characteristics of human PNP. It is often used to test the effectiveness of neuroprotective and pain-relieving treatments [6, 7]. All the parameters of behavioral studies used to check the changes in behaviour and induced neuropathic pain. [22]. This study investigated the therapeutic efficacy of FA and ALA, both of which possess significant anti-inflammatory and antioxidant properties, both individually and synergistically in a PSNL-induced PNP model, relative to the standard medication gabapentin [35]. ALA is a naturally occurring organosulfur molecule that works with other molecules in the mitochondria to help them work better. It is known for its ability the to scavenge ROS and regenerate endogenous antioxidants like glutathione, and boost mitochondrial activity [12,36]. FA is a phenolic molecule made from plants that has strong antioxidant properties, keeps cell membranes stable, and stops inflammatory mediators like the MAPK and NF-κB pathways that are involved in neuropathic pain signaling [14,37]. The combination of ALA and FA is based on how they work together: FA helps stabilize membranes and change inflammatory pathways, while ALA mostly lowers oxidative stress inside cells and restores redox balance. Gabapentin, a commonly used first-line medication for neuropathic pain, binds to the α2δ subunit of voltage-gated calcium channels to lower the release of excitatory neurotransmitters. However, because it doesn't work very well and has side effects, other treatments or therapies should be looked into [38].

In this experimental model, PSNL effectively elicited neuropathic pain in male Wistar rats, as evidenced by notable behavioral deficits. The disease control group showed a steady worsening of neuropathic symptoms over the 29-day study period, which showed that the model was successfully created. Gabapentin treatment markedly enhanced behavioral outcomes, confirming its efficacy as a standard control [39]. The von Frey test exhibited significant mechanical allodynia in PSNL rats, indicated by reduced paw withdrawal thresholds. Gabapentin effectively reversed these responses, aligning with its established analgesic properties [40]. Treatment with ALA and FA separately led to moderate improvement, while their combined use had a stronger effect, which suggests that they work together to change how the body feels pain. Similar findings were noted in the acetone test employed to assess cold allodynia. Animals with PSNL were more sensitive to cold stimuli, and treatment with ALA and FA alone only helped a little. The combination therapy significantly brought withdrawal latency back to normal levels, which means that it improved the control of cold-sensitive nociceptors and ion channel activity [41]. In the pinprick test for mechanical hyperalgesia, animals with the disease showed stronger withdrawal responses. Gabapentin effectively normalized this hypersensitivity, while ALA and FA exhibited moderate effects individually, demonstrating enhanced efficacy when administered concurrently.

In this experiment, PSNL successfully caused neuropathic pain in male Wistar rats, which was shown by major changes in their behavior. The neuropathic symptoms of the disease control group got worse over the 29-day experiment, which suggests that the model was successfully created. The significant enhancement in behavioral outcomes post-treatment validated the application of gabapentin as a standard control [39]. The von Frey test showed that PSNL rats had a lot of mechanical allodynia because their paw withdrawal thresholds were lower. Gabapentin was able to successfully stop these reactions, which is in line with what we know about its pain-relieving effects [40]. Giving ALA and FA together made things better more than giving them separately, which suggests that they work together to change how the body feels pain.

Cold allodynia assessed to check with acetone test, gives the similar results. Treatment with ALA and FA alone helped a little, but PSNL animals were more sensitive to cold. The combination treatment brought withdrawal latency back down to baseline levels, which means that ion channel activity and cold-sensitive nociceptors were better controlled [41]. In the pinprick test used to measure mechanical hyperalgesia, animals with disease control showed stronger withdrawal reactions. Gabapentin worked well to bring back this hypersensitivity, but ALA and FA didn't do much on their own and worked better when taken together.

The behavioral and biochemical outcomes were additionally validated by histopathological evidence. Axonal degeneration, demyelination, and inflammatory infiltration were characteristic features of neuropathy observed in sciatic nerve slices from the disease control group [8]. Gabapentin treatment made the structure a little better. Giving ALA and FA separately only partially restored nerve integrity. However, giving them together resulted in nearly normal architecture with intact axonal structures, less inflammation, and retained myelin, showing their potential to protect nerves in a synergistic way [45]. The better effect seen when ALA and FA are combined may be due to the fact that they work both to target oxidative stress, mitochondrial malfunction, inflammation, other parts of neuropathic pain. FA stabilizes lipids in membranes and stops inflammation pathways, while ALA boosts the body's ability that fight oxidative stress, improve mitochondrial function [46, 47]. This combination action protects the brain better than gabapentin alone or standard treatment.

CONCLUSION:

Peripheral neuropathic pain (PNP) is a significant therapeutic concern due to the variety of their complex factors, including the oxidative stress, and inflammatory responses, and neuronal sensitization. The need for alternative or additional therapeutic approaches is demonstrated by the fact that conventional treatments, such as gabapentin, are frequently advised but only partially alleviate symptoms and may have adverse effects. In this regard, the current study investigated the potential of two natural substances, FA and ALA, in a validated preclinical model of PNP caused by PSNL. Both their individual an combined effects was assessed, and they were compared to the widely used drug gabapentin. The results confirmed the successful development of chronic neuropathic pain using the PSNL paradigm in Wistar rats, as demonstrated by persistent behavioral symptoms such as mechanical and cold allodynia, mechanical and thermal hyperalgesia. Because these features closely resemble clinical neuropathic pain situations, they validate the model's reliability. The disease control group's prolonged nociceptive responses and significant biochemical and histological alterations provided additional evidence for the successful model

establishment.

Gabapentin significantly improved behavioral metrics as a standard reference and partially treated oxidative and inflammatory disorders. However, it primarily had symptomatic effects and had little effect on underlying cellular damage. Conversely, both ALA and FA demonstrated potent neuroprotective and anti-nociceptive properties. When administered separately, each chemical improved oxidative balance and pain-related behaviors, but when administered in combination, the benefits were more pronounced, indicating a synergistic interaction that targets multiple pathogenic processes. The combination treatment was more effective at reversing the alterations in pain perception brought on by PSNL, according to behavioral tests. Improvements were seen in the all behavioural parameters, but the better responses in the hot plate test indicated a recovery of thermal nociception. These results were more significant with the combined treatment than with either gabapentin or individual therapies, suggesting that concurrent regulation of oxidative stress and inflammation provides greater therapeutic benefit. Biochemical analyses supported these conclusions. PSNL damage led to increased lipid peroxidation, as evidenced by increased malondialdehyde (MDA), as well as decreased levels of antioxidants such as GSH, SOD, and CAT. While gabapentin only slightly improved antioxidant defenses, treatment with ALA and FA significantly restored them, especially when combined. The combo therapy effectively increased antioxidant enzyme activity and decreased oxidative damage, indicating improved redox equilibrium. It was also clear that the treatments had the capacity to reduce inflammation (anti-inflammatory). Anti-inflammatory therapies were also used. TNF-α, a key modulator of neuropathic pain, was significantly higher in the PSNL group. Both ALA and FA significantly reduced TNF-α levels, with the combination group exhibiting the largest decrease. The suppression of inflammatory signaling pathways, like MAPK and NF-κB, which enhances nerve function and reduces neural sensitization, explains this effect. Results from biochemistry and behavior were consistent with those from histopathology. In the disease control group, axonal degeneration, demyelination, and inflammatory infiltration were all clear signs of nerve injury. Gabapentin therapy resulted in a moderate structural improvement, whereas ALA and FA demonstrated greater preservation of nerve architecture. The near-normal histological features of the combination therapy showed strong neuroprotective benefits and prevention of structural damage. Overall, the combination of ALA and FA provides a useful treatment approach by addressing multiple aspects of neuropathic pain pathophysiology. ALA primarily enhances intracellular antioxidant capacity and mitochondrial function, whereas FA aids in membrane stabilization and reduces inflammatory pathways. By effectively addressing oxidative stress, inflammation, and neuronal dysfunction, their combination offers superior neuroprotection compared to either monotherapy or conventional gabapentin treatment. Because of their natural origin and favorable safety characteristics, ALA and FA show promising potential for therapeutic use. Further studies on pharmacokinetics, optimal dosage, and long-term safety in humans are required. Additionally, when used as an adjunct therapy in addition to existing neuropathic pain medications, they may improve therapeutic outcomes while lowering side effects.

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all the Authors claim no conflicts of interest in this present research work.

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STATEMENT ON DATA AVAILABILITY:

This published article has all the information that was gathered or looked at during this study.

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