RESEARCH PAPER

Neuroprotective Effects of Alpha-Lipoic Acid and Ferulic Acid on Chronic Constriction Injury Induced Peripheral Neuropathic Pain in Rats

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ABSTRACT

Background: Peripheral neuropathic pain (PNP), a persistent and incapacitating illness caused by nerve injury or metabolic imbalances, is characterised by increased nociceptive sensitivity and neuroinflammation. A model of chronic constriction injury (CCI) in rats closely resembles PNP in humans. Alpha-lipoic acid (ALA) and ferulic acid (FA), two naturally occurring antioxidants, have potent neuroprotective and anti-inflammatory properties. This work investigated and compared the therapeutic potential of ALA, FA, and their combination with the popular drug gabapentin in a CCI-induced PNP model in rats.

Methods: Five adult groups (n=6) Group I: Disease Control, Group II: Gabapentin (30 mg/kg, i.p.), Group III: alpha-lipoic acid (25 mg/kg, p.o.), Group IV: ferulic acid (10 mg/kg, p.o.), and a combination of Group V: alpha-lipoic acid + ferulic acid (12 mg/kg + 5 mg/kg, p.o.) were administered to Wistar rats. The behavioural assessments included mechanical allodynia (von Frey), cold allodynia (acetone), thermal allodynia (hot plate), and mechanical hyperalgesia (pinprick). Biochemical analyses assessed SOD, CAT, GSH, MDA, and TNF-α levels in sciatic nerve homogenates, while histopathological analysis assessed axonal integrity and inflammation.

Result: CCI significantly increased oxidative stress, pro-inflammatory markers, and nociceptive behaviour. Small improvements were seen with ALA or FA alone. Nevertheless, their combined effects were very similar to gabapentin's, considerably lowering pain behaviour and returning oxidative and inflammatory indicators to normal. Histology demonstrated improved axonal preservation in combination-treated rats.

Conclusion: ALA and FA's synergistic neuroprotective and antioxidant properties, especially when combined, suggest that they may be used as an adjuvant or alternative treatment for PNP.

Keywords: TNF-α; Alpha-Lipoic Acid; Ferulic Acid; Antioxidant Therapy; Chronic Constriction Injury; Peripheral Neuropathic Pain

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Introduction

Peripheral neuropathic pain (PNP) is defined as pain is arises directly from a lesion or disease affecting the somatosensory nerve system [1]. Clinical definition includes allodynia (pain generated by ordinarily non-painful stimuli), hyperalgesia (an enhanced reaction to painful stimuli), dysesthesia, paraesthesia, and spontaneous pain. These signs mean that the pain threshold has gone down and that the brain is processing sensory data in a abnormal way [1,2]. International Association for the Study of Pain (IASP) revised the concept of neuropathic pain to emphasise its neurological basis and distinct pathophysiology compared to nociceptive pain types [1]. Epidemiological studies indicate that approximately 6–10% of the general population experiences neuropathic pain. It is more prevalent among the elderly and individuals with diabetes, severe nerve injury, or post-herpetic neuralgia [2,3]. Large population-based studies have indicated that over 20% of people with chronic pain have neuropathic symptoms. This shows how big of an influence it has on quality of life and the economy [3]. Neuropathic pain (NP) lasts a long time and is associated to sleep issues, sadness, and the

inability to complete everyday tasks. This raises healthcare costs and disability-adjusted life years around the world [2].

The basic processes that cause PNP are complex peripheral and central sensitisation processes that happen when a nerve is injured [4]. Damage to peripheral nerves leads to ectopic impulse production and alterations in the expression of voltage-gated sodium and calcium channels, particularly Nav1.7 and Nav1.8. This makes neurones more likely to fire and reduces the threshold for them to do so [4,5]. Increased calcium influx enhances glutamate release in their dorsal horn of spinal cord, consequently amplifying nociceptive transmission and facilitating central sensitisation [4]. When synapses work better, inhibitory neurotransmission doesn't work as well, and N-methyl-D-aspartate receptors are always on, that's called central sensitisation. All of these things keep chronic pain persisting long after the injury has healed [6].

Neuroinflammation has a substantial activity in persistence of neuropathic pain [7]. After a nerve sciatic injury, macrophages, Schwann cells, and spinal microglia become active and release pro-inflammatory substances like tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6). All these substances make peripheral nociceptors more sensitive and increase excitatory synaptic transmission in the dorsal horn. This activation transcription factors nuclear factor kappa B (NF-κB) continues to make cytokines and inflammatory cascades, which keeps neurones sensitised [7, 8]. The pathophysiology of neuropathic pain is increasingly understood to be mediated by oxidative stress [9]. Peripheral nerve damage induces or stimulates the over production in reactive oxygen species and in reactive nitrogen species, results mitochondrial dysfunction, lipid peroxidation, and depletion in intrinsic antioxidant defences like glutathione (GSH) and superoxide dismutase (SOD) [9,10]. Mitochondrial failure disrupts ATP production and heightens neural excitability, consequently exacerbating hyperalgesia and allodynia [10]. Experimental data indicates that pharmacological scavenging of reactive oxygen species (ROS) mitigates mechanical and thermal hypersensitivity, hence validating the causal association of oxidative stress in neuropathic sensitisation [9].

The CCI model of sciatic nerve is among the most rigorously confirmed experimental frameworks for investigating neuropathic pain processes [11]. CCI causes partial nerve damage that results in Wallerian degeneration, demyelination, endoneurial oedema, and the infiltration of inflammatory cells. This closely resembles the pathology seen in clinical neuropathy [11,12]. Mechanistically, CCI causes pro-inflammatory cytokines to be produced more, ROS to be produced more, NF-κB signalling to be turned on, and ion channel expression to change in damaged fibres. This leads to long-lasting mechanical allodynia and thermal hyperalgesia [12,13]. Reduced antioxidant enzyme activity and elevated malondialdehyde (MDA) levels in CCI rats substantiate the role of oxidative damage in pain exacerbation [13].

Since oxidative stress and inflammation are so important in PNP, antioxidant-based treatments have gotten a lot of attention [9]. Alpha-Lipoic Acid (ALA) is a naturally occurring dithiol molecule that acts as co-factor for an mitochondrial complexes α-ketoglutarate dehydrogenase and pyruvate dehydrogenase. It is also a very strong antioxidant [14]. ALA and their reduced form that’s dihydrolipoic acid, directly eliminate RNS and ROS, regenerate endogenous antioxidants including vitamins C and E, and recover intracellular glutathione levels [14,15]. Also, ALA stops NF-κB from being activate and lowers production of inflammatory cytokines. This means that it has neuroprotective effects and anti-inflammatory in models in neuropathy [15, 16]. Clinical investigations in diabetic neuropathy have shown that ALA speeds up nerve transmission and eases neuropathic symptoms, which supports its relevance in the real world [16]. Ferulic Acid (FA) is a phenolic antioxidant that is found in many plant cell walls and is known for its ability to get rid of free radicals [17]. FA protects cell membranes by stopping lipid peroxidation and neutralising hydroxyl and peroxyl radicals by giving them hydrogen atoms [17,18]. FA also turns on Nrf2 that’s nuclear factor erythroid 2–related factor 2 that the signalling pathway, makes the antioxidant enzymes like heme-oxygenase-1 (HO-1) and SOD more active [18]. Experimental studies indicate that FA suppresses NF-κB-mediated inflammatory signalling and reduces cytokine production, thereby attenuating neuroinflammatory damage and neuronal apoptosis [18,19]. In this present study, utilised CCI model in rats to simulate chronic neuropathic pain. We wanted to see how well ALA and FA could preserve nervous system and act as antioxidants. We were also interested in how well they may be used as a new way to treat Peripheral Nerve Injury (PNI).

MATERIAL AND METHODS

Drugs

In this present study utilised Gabapentin from The Maharaja Sayajirao University of Baroda, Baroda,

India (gift sample), FA from Otto-Kemi Pvt. Ltd. (gift sample), and ALA from Sigma-Aldrich (gift sample). All additional reagents and chemicals used in this study were of good quality and obtained from certified and reputable supplier to guarantee the reliability and repeatability of the experiments.

Lab animals

In this study utilised healthy adult Wistar rats (male), each weigh between 200 to 250 grams. We got the animals from the Lakshmi Biofarms Animal House in Pune, MS, India (Disease-Free). The rats kept in a normal lab setting, which include temperature (22 ± 2 °C), and humidity (50 to 60%), their cycle 12-hour of light/12-hour of dark. Animals were given a regular pellet meal (VRK Nutritional Solutions, Sangli, India) and as much water as they wanted. Institutional Animal Ethics Committee (IAEC) of The Scitesla Pvt. Ltd. in Navi Mumbai, MS, India, examined and the approved experimental protocol (Approval No.: SCI / IAEC / 2024 - 25 / 142). Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), and Climate Change, Government of India, and Ministry of Environment, Forests, established criteria that were followed in all experimental operations.

Drug Solution Preparation

For administration, gabapentin was dissolved in normal saline (NS) [20]. According to recognised protocols [21], ALA and FA were made fresh in normal saline before being given. All medication solutions were newly produced on the day of experimentation to guarantee stability and pharmacological effectiveness.

Surgical Procedure

The CCI approach established by Bennett and Xie (1988) was used to cause peripheral neuropathy. There were six Wistar rats in each of five groups. A small cut was made in middle section of the thigh region to expose sciatic nerve through their biceps femoris muscle while individual was under ketamine–xylazine anaesthesia. A short muscle twitch was detected after three to four loose 4-0 silk ligatures were positioned around 7 mm section of sciatic nerve proximal to its trifurcation, spaced 1 mm apart. Animals were observed for two weeks after the incision was sutured and given the proper postoperative analgesics. After the neuropathic pain paradigm was set up, rats were given FA, ALA, or gabapentin once a day for 14 days. Behavioural evaluations were performed on day 15 post-surgery and day 29 after the conclusion of treatment [22].

Experimental Plan

In this investigation, pharmacological treatments commenced subsequent to the effective induction of neuropathic pain and persisted for two weeks following CCI surgery, resulting in a total treatment duration of 14 days post-induction. As the disease control group, Group I Disease Control was received normal saline orally. Gabapentin (30 mg/kg, IP, once daily) for Group II, which is regarded as the standard therapy group, for 14 days following the induction of neuropathy. For the same duration, Group III was administered α-lipoic acid once daily (25 mg/kg, orally). Group IV received ferulic acid (10 mg/kg, oral, once daily). Group V received combination therapy of ferulic acid (5 mg/kg) and α-Lipoic acid (12 mg/kg), given orally (one dose on each day) for 14 days after CCI induction. The objective of this experimental protocol was assess, compare to neuroprotective efficacy of ferulic acid and α-lipoic acid, and in both delivered separately and in conjunction, against CCI-induced PNP in rats, with gabapentin drug as for standard treatment.

Name of Group	Animal count	Drug therapy	Administration method	Drug dosage (mg/kg)	Duration of drug treatment
Group I: Disease Control	Six	N.S.S.	Oral administration	-	14 Days
Group II: Gabapentin	Six	Gabapentin	Intraperitoneal	30	14 Days
Group III: ALA + CCI	Six	ALA	Oral administration	25	14 Days
Group IV: FA + CCI	Six	FA	Oral administration	10	14 Days
Group V: FA + ALA + CCI	Six	ALA + FA	Oral administration	12 + 05	14 Days

Table no. 1. Grouping of animals.

Evaluation of behavioural parameters

Rats were not subjected to a stressful environment during in this behavioural testing, and these studies conducted from 09.00 am to 03.00 pm.

Evaluation of Mechanical Allodynia method Using the von Frey Filament

Using von Frey filaments and a standardised process, mechanical allodynia was assessed. Before testing, each rat was allowed to acclimatise for 15 to 30 minutes in a clear enclosure that was set up on the elevated wire mesh platform. On plantar surface of hind paw, calibrated monofilaments by weighing between the 0.4 and 15 g were applied perpendicularly. Each of these filaments was held in place for 1 to 2 sec. after being the gently squeezed until it should be slightly bent. If the animal showed signs of shaking, licking, or paw withdrawal, this was noted as a favourable response. When testing began, a filament with medium range weight usually 2.0 g was typically use. Subsequent filaments with varying forces were chosen based on the animal's reaction; if no response was seen, the force was lower; if a response was shown, the force was stronger. The up-down approach was used to the calculate the 50 % paw withdrawal threshold (PWT). The purpose of this evaluation was to evaluate the development or attenuation of mechanical allodynia following nerve injury or pharmacological treatment. It was carried out on specific days [23].

Evaluation of Cold Allodynia Using the Acetone Test

The acetone drop method, a well used behavioural assay in NP, use to assess cold allodynia. Using fine tipped applicator, a tiny amount of 99.7% 20 µL acetone was carefully applied to glabrous skin area directly beneath ears, making sure that there was no excessive pressure or dripping. Each animal was monitored for nociceptive behaviours, such as paw withdrawal, quick head shaking, grooming, or scratching, for 60 seconds after application. These reactions were seen as pain and/or discomfort by cold. To the reduce tension and the guarantee accurate behavioural observations, treatment is carried out in calm and regulated setting. In this technique made it possible to measure cold allodynia sensitivity and analyse analgesic effects of NP condition therapies [24–26].

Pinprick Test for Mechanical Hyperalgesia Evaluation

The pinprick stimulation approach, which is often used in established the pain model and this model used to measure mechanical hyperalgesia. This method allows without penetrating to skin, using sterile safety pin and carefully put to lateral surface of afflicted hind paw. This did not involve any penetration of the skin. The pressure used was enough to make a little indent, and the length of time it took for the paw to come back was used as the reaction measure.

To prevent too much stress or harm to the tissue, a maximum cut-off period of 15 seconds was specified, and responses less than 0.5 seconds were not counted. Each animal went through three distinct tests, with enough time between each one for the animals to recover. We figured out the average of the three readings so we could look at them again. The measure of mechanical hyperalgesia under neuropathic pain circumstances that was provided by this method was reliable and reproducible [27].

Thermal Allodynia Evaluation Utilising Eddy's Hot Plate Technique

Eddy's hot plate method, well-known way to measure nociceptive thresholds in rodents, was used to test for thermal allodynia [28]. We put each rat on its own hot plate that stayed at steady temperature of 55 ± 0.1°C. The latency period, which is the time passed before the first observed pain related behaviour, including flicking a paw, licking a paw, or jumping, was measured in seconds. A stringent cut off time 18 seconds was set to the avoid heat harm. Animals that failed to demonstrate a nocifensive response within this timeframe were immediately removed from the apparatus to prevent tissue damage.

All tests were done in controlled settings to make sure they were the same each time. The measured delay values were utilised to ascertain modifications in thermal sensitivity linked to neuropathic pain and subsequent therapeutic interventions.

Evaluation of oxidative stress (intrinsic antioxidant defence)

Homogenisation Parameters for Tissue

Following the conclusion of the treatment regimen, animals were euthanised, and sciatic nerve was meticulously dissected and excised. The removed tissue was promptly in the ice-cold Tris-HCl buffer (pH 7.4). The specimen was thereafter finely chopped using sterile surgical blade put into cooled sucrose solution (0.25 M). Thereafter, the tissue samples were homogenised at low temperatures in a Tris-HCl buffer (pH 7.4, 10 mM, 10% w/v). Homogenate underwent centrifuge at 10,000 rpm for the 15 minutes at 0°C [29,30]. Transparent supernatant acquired post-centrifugation was gathered for biochemical assessment of the oxidative stress indicators and the cytokine concentrations.

Reduced Glutathione (GSH) Estimation

A spectrophotometric approach published by Moron et al. [31] was used to find out how much reduced glutathione (GSH) was in tissue samples. The sulfhydryl group in GSH mixed with 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB) to create the yellow chromogen and detected at 412 nm. To prepare the sample, the tissue supernatant was combined with an equal amount of 20% trichloroacetic acid to make proteins fall out of solution. The clear supernatant was collected for analysis after the centrifugation. We mixed supernatant (0.25 ml) with DTNB (2 ml) and measured absorbance of the colour that formed at 412 nm. The findings were quantified in micrograms of GSH per milligram of protein.

Estimating the Activity of Superoxide Dismutase (SOD)

SOD is important antioxidant enzyme and that protects the cells by changing superoxide radicals into less reactive molecules. This stops adrenaline from turning into adrenochrome. Distilled water diluted tissue homogenate equally. Then, ice cold ethanol (0.25 ml) and chloroform (0.15 ml) were mix to the diluted sample. After five minutes of cyclo-mixing, the mixture was centrifuge at the 2500 rpm. A total of 0.5 millilitres of the clear supernatant were extracted from the solution that was produced, and then it was mixed in carbonate buffer (1.5 ml), and EDTA (0.5 ml). A volume of 0.4 millilitres of epinephrine was added to start the reaction. We evaluated the change in absorbance at 480 nm and reported SOD activity in the units per milligram of protein [32].

Estimating the Activity of Catalase (CAT)

We used the method explained by Aebi to measure rate of the hydrogen peroxide (H_2O_2) decomposition to determine out how active catalase (CAT) was in sciatic nerve tissue [33].

For the test, 1 ml tissue supernatant combined with phosphate buffer (1 ml) with their pH 7.0 (concentration was 50 mmol/L). The reaction started when H_2O_2 (1 ml of 30 mmol/L) was add in 2 ml of sample mixture that had already been made. Over time, the absorbance steadily dropped, showing that enzymes were breaking down H_2O_2. Activity of CAT measured by amount of hydrogen peroxide that broke down/minute for every milligram of protein [34].

Estimating Lipid Peroxidation: Malondialdehyde (MDA)

MDA method levels were measured to assess tissue lipid peroxidation using Slater and Sawyer's approach [30]. To make proteins fall out of solution, tissue supernatant (1-2 ml) was combined with the trichloroacetic acid (10% w/v), put in an ice cold water bath for the 15 min. Then, the mixture was spun in a centrifuge to get a clear supernatant. After that, 2 ml of a thiobarbituric acid solution (freshly made) was add in the supernatant. For 10 minutes, this mixture heated in boiling water bath then let colour develop. Then, it was quickly cooled on ice for 5 minutes. The coloured complex's absorbance was observed and measured at 532 nm using spectrophotometer and a reagent blank. We established a standard curve using known amounts of MDA and then determined the levels of MDA in nanomoles of MDA/milligram of the protein.

Evaluation of inflammatory markers

Determining the Level of Tumour Necrosis Factor-α (TNF-α)

We used ELISA kit to measure levels of TNF-α in the sciatic nerve tissue, following this method reported by Muthuraman [35]. Test used a specific anti-TNF-α antibody to find things. We prepared TNF-α standard solutions and their concentrations from an 0 to 20,000 pg/ml to make calibration curve. We use a microplate reader for evaluate the strength of the yellowish colour is formed after the reaction at 450 nm. We used the standard curve to figure out the final TNF-α concentrations in tissue homogenates and reported them as picograms of the TNF-α per milligram of the total protein.

Sciatic Nerve's Histopathology

Following the completion of the treatment, the rats were put into anesthesia and then sacrificed in order to collect the tissues that were found in the sciatic nerve. To keep the nerves' structure and cells intact, they were quickly preserved in the 10% formalin. Tissues were cut into 4 mm thick slices once they had been properly fixed. The sections were treated and the stained with haematoxylin and the eosin for histological analysis. Subsequent evaluation of morphological changes and neuropathological characteristics was conducted using a light microscope [36].

Statistical Examination

All the data were shown as mean ± standard deviation (SD) for six animals in each group (n = 6). We used analysis of variance (two-way ANOVA) for the statistical analysis, and then we used Bonferroni post hoc testing to compare the results. A value of $P<0.05$ was statistically significant.

RESULTS

Mechanical Allodynia (von Frey Filament-Induced): How ALA and FA Work

We measured mechanical allodynia after CCI-induced neuropathy by looking at the paw withdrawal latency

(PWL) caused by von Frey filaments. On Second reading Day 15 (4.16 ± 0.74 sec) and last reading Day 29 (4.10 ± 0.88 sec), the group II disease control had a significant drop in PWL compared to Day 0 (###p < 0.001), which confirmed that mechanical allodynia had been successfully induced. Gabapentin treatment significantly reversed this deterioration, with PWL of 8.01 ± 0.56 sec on last reading Day 29 (***p<0.001 compared to group I disease control). Administration of ALA (Group III) significantly enhanced sensitivity and increasing PWL to 8.51 ± 1.03 sec (***p < 0.001 vs. group I disease control). Ferulic acid (Group IV) treatment also led to a PWL of 8.50 ± 1.03 sec (***p<0.001 vs. group I disease control). Group V resulted in most significant enhancement, restoring PWL in reading to 9.27 ± 0.97 seconds by last Day 29 (***p < 0.001 vs. group I disease group), indicating a synergistic and neuroprotective effect in this method.

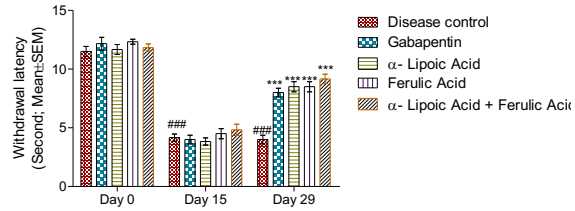

Figure 1: We used von Frey filaments to measure PWL on Days 0, 15, and 29 to see if there was mechanical allodynia. Data are presented the mean ± SEM (n = 6), were analyzed using ANOVA (two-way) and the Bonferroni post-hoc method. *p<0.05, **p<0.01, ***p<0.001 compared to group I disease control; ###p < 0.001 compared to first Day 0. PWL significantly decreased in group I disease control on Days 15 and Day 29 compared to first Day 0 (###p < 0.001), which means that mechanical allodynia was developing. Group II significantly increased PWL on last Day 29 (***p<0.001), indicating a decrease in hypersensitivity. There were also very strong protective benefits from Group III (***p<0.001), Group IV (***p<0.001), and the Group V (***p<0.001). The Group V was the most effective at reversing von Frey induced mechanical allodynia.

Acetone Test by Cold Allodynia method: Impact of ALA and FA

We measured acetone-evoked paw withdrawal latency (PWL) to find out if there was cold allodynia after CCI-induced neuropathy. PWL significantly decreased in group I disease control on Days 15 and 29 (11.01 ± 2.23 sec) compared to Day 0 (45.73 ± 8.69 sec), indicating cold allodynia development (###p<0.001 vs. first Day 0). In Group II significantly elevated PWL by last Day 29 (27.51 ± 5.74 sec, ***p < 0.001 vs. group I disease control), showing reduction in cold hypersensitivity. Ferulic acid (23.84 ± 4.63 sec, **p<0.01 vs. group I disease control) and α-lipoic acid (26.66 ± 5.12 sec, **p<0.01 vs. group I disease control) also made cold sensitivity much better. Combining ALA and FA led to a significant increase in PWL (42.67 ± 4.64 sec) (***p<0.001 vs. group I disease control), and indicating synergistic augmentation in cold allodynia reversal.

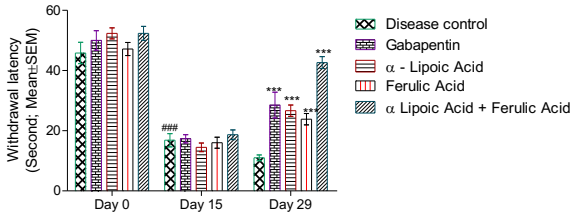

Figure 2: PWL measurements were conducted on first reading Days 0, second reading day 15, and last reading day 29 to evaluate cold sensitivity. This data is presented in mean ± SD (n = 6), were analyzed using a ANOVA (two-way) method followed by a Bonferroni post-hoc method. *p<0.05, **p<0.01, ***p<0.001 in comparison to the group I disease control. The group I disease control experienced a substantial decline in PWL on second reading Day 15 and third reading Day 29 compared to first reading Day 0 (###p < 0.001), which showed that cold allodynia had started. Treatment with Group III, IV and V largely reversed the decrease, with the Group V showing the good efficacy.

Pinprick Test for Mechanical Hyperalgesia: Impact of ALA and FA

Mechanical hyperalgesia was measured by pinprick-induced paw withdrawal latency (PWL). In group I disease control, there is a significant drop in PWL from first reading Day 0 (11.20 ± 0.72 sec) to second reading Day 15 (5.26 ± 0.79 sec) and last reading Day 29 (4.83 ± 0.81 sec). This shows that mechanical hyperalgesia was developing (###p < 0.001 vs. Day 0). Gabapentin treatment significantly augmented withdrawal latency (9.71 ± 1.11 sec, ***p<0.001 compared to group I disease control). α-Lipoic acid (9.61 ± 0.83 sec, ***p<0.001 vs. group I disease control) and ferulic acid (9.66 ± 0.91 sec, ***p<0.001 vs. group I disease control) significantly enhanced PWL. The combination treatment with FA and ALA resulted in a significant increase in PWL (10.04 ± 0.54 sec, ***p<0.001 vs. group I disease control), indicates the synergistic response in the decreasing mechanical hyperalgesia.

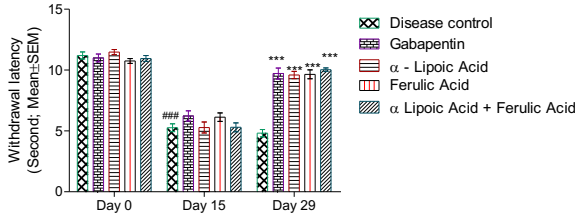

Figure 3: We assessed the time it took for CCI-induced neuropathic rats to pull their paws away from pinprick stimulation on the Day 0 next on Day 15 and last on Day 29. We employ ANOVA (two-way) and the Bonferroni post-hoc method to look at the data and provided as mean ± SD (n = 6). *p<0.05, **p<0.01, and ***p<0.001 when compared to group I disease control. The group I disease control had significantly reduction in latency on the Day 15 and last day 29 compared to first Day 0 (###p < 0.001), this indicating the progression of the mechanical hyperalgesia. ALA, FA, Standard Gabapentin and their combination (ALA, FA) all significantly increased withdrawal latency on last Day 29. The group V had the strongest protective impact.

Eddy's Hot Plate Method for Thermal Allodynia: The Impact of ALA and FA

The PWL measured on the first time on day 0, Second data gathered on day 15, and third data gathered on day 29 to see if thermal allodynia was present by this method. The group I disease control much reduced PWL on Days 15 (4.01 ± 0.63 sec) and 29 (2.34 ± 1.20 sec) compared to baseline values (13.65 ± 1.22 sec) (###p < 0.001 vs. Day 0) showed that heat hypersensitivity had developed following CCI. Gabapentin treatment made PWL go up a lot, reaching 9.00 ± 1.09 seconds on Day 29 (***p<0.001 vs. group I disease control). Treatment with α-lipoic acid and ferulic acid also significantly improved PWL, with recorded values of 4.66 ± 1.08 seconds and 6.18 ± 1.71 seconds, respectively (***p<0.001 vs. group I disease control). When FA and ALA were given simultaneously, the most improvement was seen. On Day 29, PWL was 9.66 ± 1.50 seconds (***p<0.001 compared to group I disease control), which suggests that two drugs worked together to relieve pain.

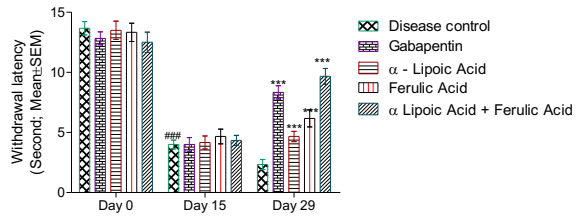

Figure 4: We used Eddy's hot plate to measure the time it took for the paw to pull away on treatment days for first data gathered on day 0, Second data gathered on day 15, and third data gathered on day 29 to check for thermal allodynia and for treatment of drugs. We employ ANOVA (two-way) method and the Bonferroni post-hoc method to look at the data, which are provided as mean ± SD (n = 6). *p<0.05, **p<0.01, and ***p<0.001 when compared data to the group I disease control. The group I disease control had a decreased the levels in PWL on the Days 15 and 29 compared to Day 0 (###p<0.001), which showed that thermal allodynia had developed. Treatment with group II gabapentin (***p<0.001), FA (***p<0.001), and ALA (***p<0.001) made the CCI method induced drop in the PWL far less severe. By Day 29, the combination therapy had the highest effect on thermal sensitivity, which could mean that the two treatments worked better together.

The effect of ALA and FA on parameters of oxidative stress (endogenous antioxidant defense)

CCI significantly damaged the body's natural antioxidant defense system in sciatic nerve tissue. There were large decreases in superoxide dismutase (2.53 ± 0.58 U/mg protein), catalase (41.76 ± 7.80 U/mg protein), and glutathione (09.98 ± 01.50 U/mg protein), as well as a rise in malondialdehyde (10.00 ± 3.01 nmol/mg protein). This demonstrated that OS was higher. Two weeks of intraperitoneal gabapentin administration post-surgery resulted in enhanced levels of antioxidant enzymes relative to the disease control group. SOD levels rose (3.13 ± 0.70), CAT levels rose (56.89 ± 8.25, *p < 0.05), and GSH levels rose (14.30 ± 2.37), while MDA levels fell (7.50 ± 1.72).

Treatment with ferulic acid (Superoxide dismutase: 3.71 ± 0.89; Catalase: 56.95 ± 7.39, *p<0.05; Glutathione: 13.81 ± 3.09) and α-lipoic acid (Superoxide dismutase: 3.46 ± 0.80; CAT: 58.38 ± 7.18, **p<0.01; Glutathione: 15.52 ± 2.92) also significantly improved antioxidant levels while lowering MDA (7.33 ± 3.02 for FA, 5.07 ± 1.51 for ALA; **p<0.01 for the FA). Compared to group I disease control, the combination drug therapy of ALA and FA had the strongest protective effect, with highest level of Superoxide dismutase (4.09 ± 0.81, *p<0.05), Catalase (60.29 ± 7.50, **p<0.01), and Glutathione (18.30 ± 4.40, **p<0.01), and the lowest Malondialdehyde concentration (4.79 ± 3.41, **p<0.01).

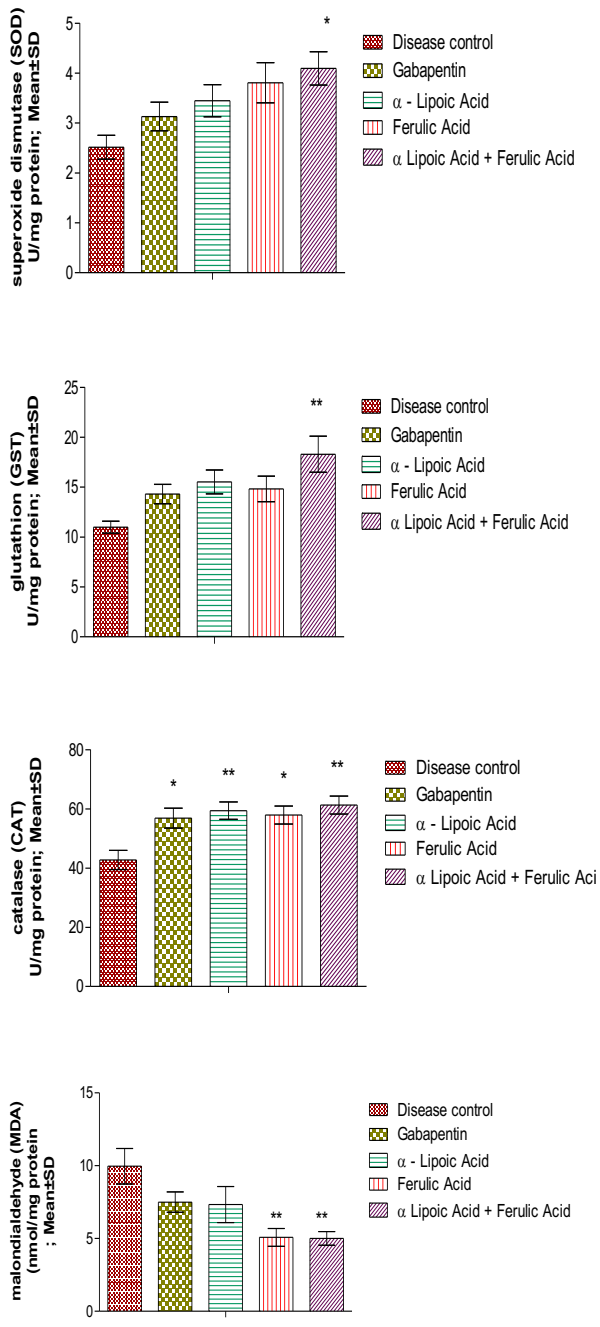

Figure 5: The impact of drug treatment in ALA and FA on antioxidant markers - 5A) Superoxide dismutase, 5B) Glutathione, 5C) Catalase, and 5D) Malondialdehyde, in sciatic nerve injury. All data provided as mean ± SD (n = 6), were analyzed using ANOVA (one-way) and subsequently the Bonferroni post hoc for interpretation. The results were statistically significant when compared to group I disease control: **P<0.01 & *P<0.05.

Effect of ALA and FA on Inflammatory Marker in Sciatic Nerve

We assessed TNF-α, a principal pro-inflammatory cytokine is increases following nerve injury, in the sciatic nerve homogenates. CCI group had large increase in TNF-α levels (68.12 ± 0.36 pg/mg protein) compared to baseline values, which demonstrated that there was a substantial inflammatory response. After surgery, gabapentin medication brought levels of TNF-α down to 31.48 ± 0.26 pg/mg protein, which was a considerable decrease.

In the same way, giving FA (32.23 ± 0.28 pg/mg, *p < 0.05) and ALA (41.95 ± 0.41 pg/mg, *p<0.05) significantly lowered TNF-α compared to the group I disease control.

FA and ALA together exhibited the highest anti-inflammatory impact, decreasing TNF-α levels to 28.97 ± 0.53 pg/mg proteins (*P<0.05 vs. group I disease control). This means that the two medications operate together to reduce neuroinflammation caused by CCI.

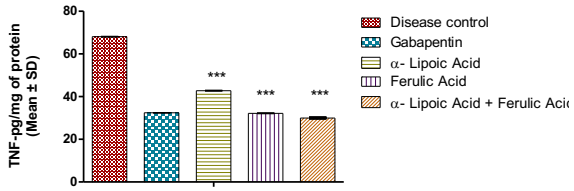

Figure 6: Effects of drug treatment ALA and FA on TNF-α cytokine levels in Wistar rats with sciatic nerve damage. All the data is presented in this test as Mean ± SD (n = 6) and interpreted using One-Way ANOVA test by using the method of Bonferroni post hoc test. The finding is statistically significant because *P<0.05 compared to the group I: disease control.

Effects of ALA and FA on the Sciatic Nerve: A Histopathological Study

Microscopic examination of sciatic nerve sections from the disease control group revealed substantial pathological alterations, including mild to the moderate infiltration of mononuclear cells, cystic enlargement of myelin sheath, and degeneration characterized by axonal loss.

The gabapentin-treated group, ALA-treated group, and the combined ALA + FA group exhibited no significant structural abnormalities, indicating considerable neuroprotective effects. The FA-treated group exhibited mild to moderate mononuclear cell infiltration, indicating a partial protective response. In general, these results support the idea that the combined therapy works better to protect the structure of sciatic nerve after CCI induced PNP.

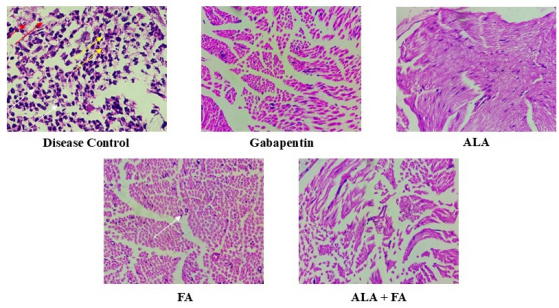

Figure 7: Histopathological alterations observed in the sciatic nerve following CCI induced PNP.

Discussion

Peripheral neuropathic pain (PNP), particularly in the CCI model, represents a well-established experimental paradigm that closely mimics clinical features such as thermal hyperalgesia, mechanical allodynia and oxidative stress–associated nerve damage [37]. In the current investigation, the effects of ALA, FA, and their combined administration were evaluated and compared with gabapentin for their antioxidant, analgesic, anti-inflammatory and neuroprotective properties. CCI is promote neuroinflammation, immune cell infiltration, and neuronal hyperexcitability, thereby intensifying pain perception in peripheral nerves [38]. Behavioral assessments conducted after CCI demonstrated a significant increase in nociceptive sensitivity. Mechanical allodynia, evaluated using von Frey filaments, confirmed enhanced tactile hypersensitivity in animals used for disease control [39]. Drug Treatments on Group III (ALA), Group IV FA, and especially their combination Group V (FA+ALA) significantly elevated mechanical withdrawal threshold, indicating attenuation of allodynia, in agreement with previous findings highlighting role of antioxidants in NP modulation [40].

Cold allodynia, investigate through acetone drop test, was also markedly increased in CCI rats, reflecting altered thermosensory processing [41]. While ALA and FA individually produced moderate improvements, their combined administration achieved effects comparable to gabapentin, suggesting synergistic neuroprotection mediated through redox stabilization and suppression of glial activation [42]. Mechanical hyperalgesia measured by the pinprick test further demonstrated reduced withdrawal responses in treated groups, with the ALA+FA combination showing superior antihyperalgesic activity [43]. Additionally, Eddy's Hot Plate Method for Thermal Allodynia evaluated and revealed prolonged latency in treated animals, confirming restoration their pain thresholds [44].

Oxidative stress is a important part in onset of CCI-induced neuropathy. After an injury, mitochondrial dysfunction and the entry of immune cells into the body increase production of ROS, which throws off redox balance [38]. In this study, CCI significantly diminished endogenous antioxidant defenses, indicated by reduced levels of SOD, CAT, and GSH, alongside increased MDA, a marker of lipid peroxidation [45]. ALA is known for its power to remove free radicals and bind metal ions. It significantly increased antioxidant enzyme levels and lowered MDA levels. The ALA+FA combination group had the strongest effect [40].

These results back up the idea that too much mitochondrial ROS production can lead to neuropathic pain by increasing calcium influx, forming peroxynitrite, and killing neurons [44]. It has been reported that both ALA and FA can change antioxidant pathways by controlling Nrf2 and blocking NF-κB signaling. This makes the body's natural defenses stronger [46]. The augmented protective effect noted with combined therapy may stem from synergistic antioxidant actions across various molecular pathways, as indicated by the near-normalization of oxidative stress biomarkers.

Neuroinflammation is another important part of how neuropathic pain starts. TNF-α, a key pro-inflammatory cytokine, makes nociceptive sensitization worse by changing the expression of ion channels, stopping axonal transport, and turning on glial cells [47]. In this study, disease control animals demonstrated markedly increased TNF-α levels in sciatic nerve tissue, thereby affirming its pro-nociceptive role [48]. Treatment drugs of ALA and FA significantly decreased the levels of TNF-α, and the combination therapy worked best, possibly because it inhibited microglial activation and cytokine transcription in a way that worked together [41].

The histopathological findings aligned with the biochemical and behavioral data. Sections of the sciatic nerve from the group I: disease control observed cystic dilation of myelin sheath, mono-nuclear cell infiltration, and the axonal degeneration, which are signs of Wallerian degeneration after CCI [43]. Conversely, tissues from the gabapentin-, ALA-, and combination-treated groups displayed intact nerve architecture, whereas FA treatment alone exhibited only minimal inflammatory infiltration. These structural findings add to the evidence that the treatments tested can protect and repair nerves. In general, these results show that ALA and FA, especially when used together, have strong pain-relieving, anti-inflammatory effects, and antioxidant in

model of neuropathic pain caused by CCI. The treated groups had a lot less pain when they were exposed to cold, heat, or mechanical allodynia. Restoring the redox balance, as shown by the normalization of SOD, CAT, GSH, and MDA levels, means that the antioxidant defense has gotten stronger. The decrease in TNF-α further validates the anti-inflammatory effectiveness of these interventions. Histological evidence finally supports functional recovery and the preservation of the integrity of the sciatic nerve.

Conclusion

The present result of this study shows ALA and FA are very effective at treating CCI-induced peripheral neuropathic pain (PNP) when given alone and even more so when given together. Behavioural tests demonstrated that the combined treatment significantly alleviated cold and Mechanical Hyperalgesia, thermal allodynia, showing efficacy to Group II: Gabapentin. Bio-chemical analyses indicated that their simultaneous administration of treatment drugs ALA and FA effectively re-established redox equilibrium by augmenting the activities of the antioxidant enzymes (like CAT, SOD, GSH), reducing LPO, as revealed by lowered MDA levels. Furthermore, the significant decrease the TNF-α, coupled with the maintenance of sciatic nerve architecture noted in histopathological examination, substantiates the anti-inflammatory and neuroprotective attributes of the treatment. Overall, these results show that ALA and FA work well together, which suggests that they could be a good addition to or alternative to current treatments for PNP.

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