Research Article

Evaluation of Combinational Therapy of L-Arginine with Some Phenolic Acids in Paclitaxel-induced Neuropathic Pain

Shubhangi Pawar[1,*], Amrapali Pagare[1], Suvarna Katti[1], Rupali Patil[1], Manisha Tayde[2]

[1]Department of Pharmacology, MGVs Pharmacy College, Panchavati, Nashik, Maharashtra, INDIA.
[2]Department of Pharm Chemistry, PES Institute of Pharmacy, Nimani, Nashik, Maharashtra, INDIA.

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Correspondence:
Shubhangi Pawar,
MGVs Pharmacy College, Panchavati, Nashik, Maharashtra, INDIA.

Email: shpawar2009@gmail.com

ABSTRACT

Background: Paclitaxel is an anticancer drug that can induce neuropathy and is used in animal models to evaluate new therapeutic approaches in neuropathy. Paclitaxel increases oxidative stress, which is a key contributor to the pathogenesis of neuropathy. Many phenolic acids as well as amino acids with antioxidant potential are proven as neuroprotective. **Objectives:** To evaluate combinational therapy of L-Arginine with Syringic acid and Sinapic acid, separately in paclitaxel-induced neuropathy by assessing behavioral and biochemical parameters. **Materials and Methods:** Wistar rats were divided into seven groups (*n*=6). Neuropathic pain was developed with Paclitaxel (2mg/kg, i.p), repetitively administered on the 1st, 3rd, 5th, and 7th days in rats. Treatment with phenolic acids, L-Arginine and Gabapentin was started along with paclitaxel from day first for 5 weeks. Behavioural study (mechanical and thermal hyperalgesia, allodynia and motor co-ordination) was carried out weekly by using Von Frey filaments, Rota rod apparatus, hot plate and cold plate. Biochemical study (MDA, GSH, SOD) was performed after sacrification at the end of the study. **Results:** A combination of L-Arginine with syringic acid and sinapic acid has shown a significant reversal of behavioural changes and oxidative stress induced by paclitaxel. L-Arginine has potentiated individual effects of syringic acid and sinapic acid. **Conclusion:** The results suggested antioxidant, analgesic and neuroprotective effects in combinational therapy of L-Arginine. This study is indicating that combination of L-Arginine could be beneficial to reduce dose requirement of syringic acid and sinapic acid in treatment of neuropathic pain.

Keywords: Paclitaxel, Sinapic Acid, Syringic Acid, L-Arginine, Neuroprotective effect.

INTRODUCTION

Cancer is a major factor in mortality worldwide. Though various anticancer drugs are available for treatment, they are associated with many adverse effects.[1] It is estimated that 30–40% of patients receiving chemotherapy eventually develop neuropathic sensory and motor disturbances.[2] Neuropathic pain may produce spontaneous or evoked responses to physical stimuli that result in increased pain sensations (hyperalgesia), and pain evoked by non-painful stimuli (allodynia). A low dose of paclitaxel can produce these symptoms in animal models.[3] Reactive Oxygen Species (ROS) is a key contributor in chemotherapy-induced neuropathy.[4] Oxidative stress generated by this drug can cause direct damage to cell components such as nucleic acids, lipids, and proteins.[5] Antioxidants, in contrast, protect the cells against the development and progression of oxidative damage.[6] Antioxidant properties of phenolic acids are not only due to their radical scavenging action but also due to their capacity to strengthen endogenous antioxidant defenses.[5]

Syringic Acid (SA) chemically is 4-hydroxy-3, 5-dimethoxybenzoic acid, an active phenolic compound that is commonly found as plant metabolite. SA

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is reported to have many therapeutic benefits as antioxidant, anti-proliferative, anti-cancer, antidiabetic and hepatoprotective activity, neuroprotective and cardioprotective effects.[7] Recently, it has been shown to increase SOD and decrease MDA, Casp-3 and Casp-9 levels and reduced oxidative stress and neuronal degeneration in SD rat brains after cerebral ischemia caused by artery occlusion.[8,9] Sinapic Acid (SP) is chemically 3,5-dimethoxy, 4-hydroxycinnamic acid. SP is extensively found in various plant sources such as rye, fruits, and vegetables. It possesses various health benefits such as antioxidant, anti-inflammatory, anticancer, antimutagenic, anti-glycemic, neuroprotective, antibacterial activities, and anti-hyperglycemic.[10] SP inhibits NF-kB activation in macrophages and further inhibits the production of iNOS, COX-2, and inflammatory cytokines, thus exerting anti-inflammatory effects.[11] Additionally, amino acid supplementation is also proven neuroprotective. Amino acid supplementation might be able to raise human performance to a restricted level. Apart from the metabolic, developmental or pathophysiological role, certain non-essential amino acids become essential. Arginine is a semi-essential cationic amino acid involved in multiple pathways in health and disease conditions. It becomes essential, under stressful conditions and metabolic disturbances where endogenous arginine synthesis is decreased in conditions like trauma, sepsis, burns and thalassemia.[12] Supplementation of L-Arginine is reported as anti-stress, anti-aging effect and adaptogenic activity.[13] L-Arginine has shown neuroprotective role in diabetic neuropathy by restoring nerve conduction.[14] So, the present work was undertaken to evaluate the combination of amino acid L-Arginine with phenolic acids syringic acid and sinapic acid in the treatment of paclitaxel-induced neuropathy.

MATERIALS AND METHODS

Wistar rats of either sex weighing around 150-200 g, were used in the study. Animals were housed under laboratory conditions as per CPCSEA guidelines. The study protocol was approved by the institutional Animal ethics committee (MGV/PC/CPCSEA/XXXVI/01/2019/05) of MGV's Pharmacy College, Nashik.

Induction of Neuropathic Pain by Paclitaxel

Animals were grouped into seven groups (n=6). Neuropathic pain was induced with paclitaxel (2mg/kg, i.p) repetitive administration on the 1st, 3rd, 5th, and 7th days. Phenolic acids, L-Arginine and Gabapentin were started along with paclitaxel from the first day of the treatment schedule for 5 weeks. After paclitaxel induction behavioral studies were carried out weekly by using Von Frey Filaments, Rota Rod apparatus, Hot Plate and Cold Plate. At the end of the treatment schedule, Biochemical and Histopathological studies were performed after sacrification.[15,16]

EXPERIMENTAL PROTOCOL

Group	Treatment given
I	Normal animals received vehicle(10mL/kg,p.o.) only.
II	Animals received Paclitaxel (2mg/kg,i.p),4 repeated doses on alternate days.
III	Paclitaxel-treated animals received a dose of Gabapentin (300mg/kg,p.o.)
IV	Paclitaxel-treated animals received a dose of Syringic Acid (SA) (25mg/kg,p.o.).
V	–Paclitaxel-treated animals received a dose of Syringic acid and l-Arginine (25mg/kg and50mg/kg,p.o respectively).
VI	Paclitaxel-treated animals received a dose of Sinapic acid (10mg/kg,p.o. respectively).
VII	–Paclitaxel treated animals received dose of Sinapic acid and l-Arginine (10mg/kg and50mg/kg,p.o.respectively).

BEHAVIORAL ASSESSMENT

Mechanical Hyperalgesia (Von Frey)

Von Frey was developed by Physiologist Maximillan Von Frey for evaluation of mechanical allodynia in rats and mice. Rat were placed on wire mesh for easy application of Von Frey filaments and acclimatized for 5 to 10 min. Filament (von Frey hairs) was applied from below the mesh floor to the planter surface of the left hind paw with sufficient force to cause slight bending against the paw and hold for sec. Application repeated 5 times repeated at intervals of 4-5 sec. Withdrawal of the left hind limb robustly immediately was considered a positive response.[17] Observations were recorded in the format of OXXOXO, where O indicated- no withdrawal response and X indicates withdrawal response. This method of observation is up and down method of Dixon and the 50% gm threshold is calculated by the formula,

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

where Xf is the log units of the last von Frey filament used; k is a tabular value for the pattern of positive/negative responses; and δ is a mean difference (in log units) between stimuli (here, 0.224).[18]

Heat Hyperalgesia (Hot Plate)

The nociceptive threshold for heat is an index for thermal hyperalgesia. The plate was preheated and maintained at a temperature of 55±2°C. The rat was placed on the hot plate and the nociceptive threshold with respect to licking of the hind paw or jumping was recorded in seconds. The onset of the licking and jumping response was recorded. The cut-off time of 20 sec was maintained.[19]

Cold allodynia (Cold Plate)

The cold plate test is the simplest method to determine behavioural responses to both noxious and innocuous cold temperatures in rodent species. Here, the rodent was placed on the cold plate at temperature4°C and the time taken to evoke nociceptive behaviour such as shaking or paw licking by the animal is recorded as the response time.[20]

Motor Coordination (Rota Rod)

Accelerating Rota Rod apparatus is used for motor coordination tests which detects neurological deficits in rats and mice. Motor in-cordination due to neuropathy causes difficulty for animals in holding a spindle of rotarod. The Arotarod spindle was rotating at a constant speed of 25 RPM and the fall time of individual rats was recorded keeping a 300 sec cut-off time.[21]

ANTIOXIDANT ACTIVITY

Preparation of tissue homogenate

The animals were sacrificed and sciatic nerve quickly isolated and transferred to ice-cold Tris hydrochloric buffered saline (pH 7.4). 10% w/v tissue was then minced and homogenized in ice-cold tris hydrochloride buffer (10mM, pH 7.4). The homogenate was centrifuged at 10,000 rpm for 15 min using Remi C-24 high speed cooling centrifuge. The clear supernatant was used to determine oxidative stress and antioxidant parameters.[22,23]

SOD (Superoxide Dismutase)

Superoxide dismutase was estimated using the method developed by Misra and Fridovich.[24] 0.5mL of tissue homogenate was diluted with 0.5mL of distilled water, to which 0.25mL of ice-cold ethanol and 0.15mL of ice-cold chloroform were added. The mixture was mixed well for 5 min and centrifuged at 2500 rpm. To 0.5mL of supernatant, 1.5mL of carbonate buffer and 0.5mL of EDTA solution were added. The reaction was initiated by the addition of 0.4mL of epinephrine and the change in optical density was measured at 480nm against reagent blank and results are expressed a % increase of SOD.[25]

GSH (Reduced Glutathione)

Equal volumes of tissue homogenate (supernatant) and 20% TCA were mixed. The precipitate was centrifuged and to 0.25mL of supernatant, 2mL of DTNB reagent was added. The final volume was made up to 3mL with phosphate buffer. The color developed was read at 412nm against reagent blank and results are expressed a % increase of RGSH.[22]

MDA (Malondialdehyde)

0.25 mL of homogenate (Tris-HCL buffer, pH 7.5) was treated with 2mLof TBA: TCA: HCL (Thiobarbituric acid 10%, TCA 15%, HCl 0.25%) and placed in the water bath for 30 min., after cooling 3mL of n-butanol was added. The solution was centrifuged at 5000 rpm for 5 min. the absorbance of clear supernatant was determined in a UV spectrometer at a wavelength of 532 nm and results were expressed % inhibition of MDA.[26]

STATISTICAL ANALYSIS

Data is expressed as mean ± SEM; analyzed by one-way ANOVA followed by Dunneet's Multiple Comparison Test (compared with the control group) analyzed by using Graph Pad Prism Version 9.0. *p<0.05, ** p<0.01 and *** p<0.001 considered as statistically significant compared to control group.

RESULTS

Behavioural studies

Mechanical hyperalgesia by von Frey hair test

Allodynia term refers to pain due to normally non noxious stimuli. In positive control group that allodynia is observed from 1st week of paclitaxel injection indicated by withdrawal response to minimum force of filament and thus decrease in 50% gm threshold. Treatment with individual dose of Syrigic Acid (SA) and Sinapic Acid (SP) in group IV and VI respectively have shown to increase force giving withdrawal response and 50% gm threshold (*p<0.05**) by changing observation format of Dixon up and down method. Combination of L- Arginine with SA and SP have shown potentiation of their effect and a significant increase in 50% gm threshold (*p<0.01***) compared to group II (Figure 1). In group III gabapentin treatment also significantly increased (*p<0.01***) 50% gm threshold compared to group II (Diseased control).

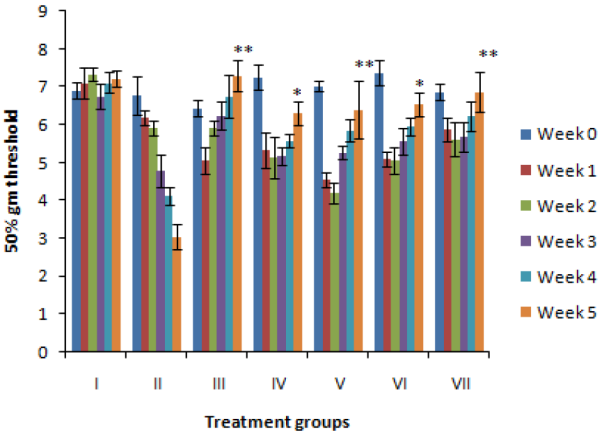

Figure 1: 50% gm threshold by Von Frey filament test.

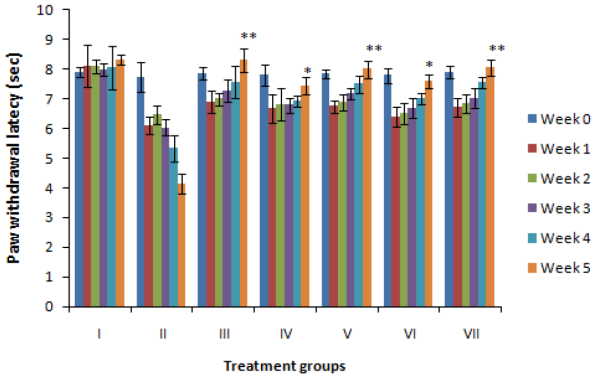

Figure 2: Paw lick latency (sec) in hot plate test.

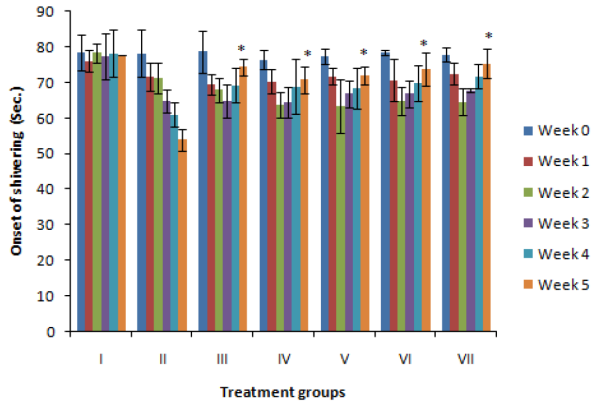

Figure 3: Onset of shivering response (sec) in cold plate test.

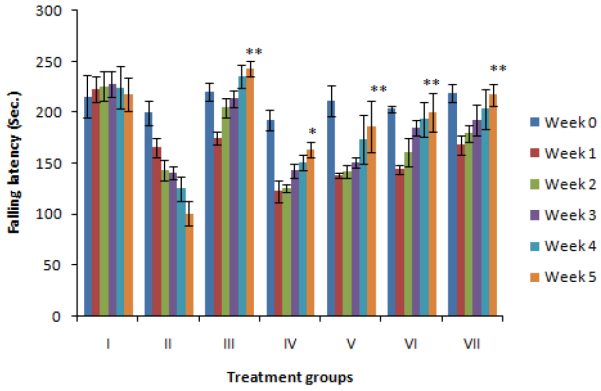

Figure 4: Falling latency (sec) from rota rod apparatus.

Heat hyperalgesia (Hot plate method)

Paw lick latency (sec)

Thermal hyperalgesia was confirmed in positive control group after 3 week of paclitaxel injection by significant fall in paw withdrawal latency (sec) as compared to negative control rats.

Treatment with individual dose of Syrigic Acid (SA) and Sinapic Acid (SP) in group IV and VI respectively have shown to increase paw withdrawal latecy significantly ($p<0.05$*) compared to group II. Combination of L-Arginine with SA and SP has shown potentiation of their effect and a significant increase in paw withdrawal latency ($p<0.01$**) compared to group II (Figure 2). In group III gabapentin treatment also significantly increased ($p<0.01$**) paw withdrawal latency on hot plate compared to group II (Diseased control).

Cold allodynia by cold plate

Cold allodynia was indicated by decrease of shivering onset (sec) in group II than I group I (normal) rats. Treatment with Gabapentin (300 mg/kg p.o), Syringic acid (25mg/kg, p.o) and Sinapic acid (10mg/kg, p.o) and their combination with l-arginine (50mg/kg, p.o) showed significant ($p<0.05$*) improvement in paw withdrawal latency (sec) after 3 week of treatment schedule as compared to group II (diseased control) rats (Figure 3).

Motor co-ordination by Rota rod

Effect of Gabapentin SA, Sp and their combination with L-Arginine on motor coordination assessed by rota rod in paclitaxel induced neuropathic pain. Single dose of Syringic Acid (SA) in group IV has shown significant ($p<0.05$*) improvement in motor coordination as indicated by increased in falling latency (sec), but it's combination with L-Arginine in group V and in group VI, VIII treatment with individual dose of Sinapic Acid (SP) and combination of SA and SP with L-Arginine respectively have improved motor incoordination with $p<0.01$** as compared to group II animals (Figure 4).

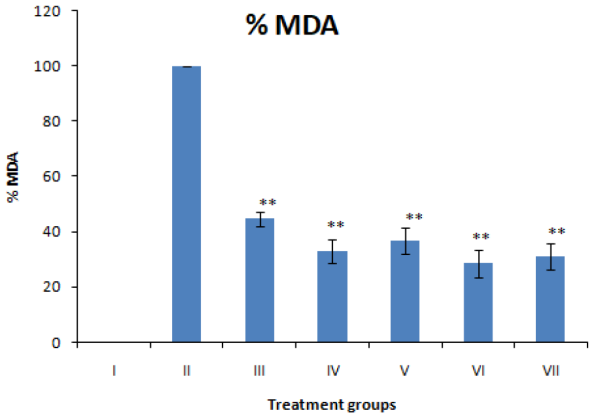

Figure 5: Percent of MDA as an indicator of lipid peroxidation.

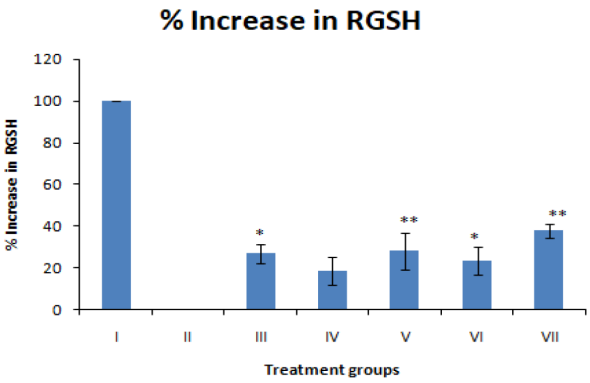

Figure 6: Percent increase in RGSH as a marker of antioxidant defense system.

ANTIOXIDANT ACTIVITY

Markers of antioxidants i.e., RGSH, SOD and oxidative stress i.e., MDA were estimated from homogenate of sciatic nerve.

Malondialdehyde (MDA)

MDA is an end product of lipid peroxidation process. Paclitaxel is known to activate lipid peroxidation of the neuronal membranes. Increase in the amount of MDA was observed in group II as compared with group I. SA, SP and combination of these phenolic acids with L-Arginine has reduced lipid peroxidation indicated by a significant reduction in MDA with $p<0.01$** as compared to group II animals (Figure 5).

Reduced glutathione (RGSH)

RGHS is the primary antioxidant in the cell significant decrease in the amount of RGHS was observed in positive control group as compared with negative control group. Treatment with gabapentin in group III and combination of syringic acid with L-Arginine in group V showed significant increase ($p<0.05$*) in RGHS level as compared to group II, Single dose of Syringic Acid (SA) in group IV have increased RGSH but in non-significant way. Sinapic Acid (SP) individually in group VI and its combination with L- Arginine in group VII indicated a significant % increase in RGHS ($p<0.01$**) compared to group II (Figure 6).

Superoxide Dismutase (SOD)

Determination is based on ability of SOD to inhibit spontaneous oxidation of adrenaline to adrenochrome. Significant decrease in SOD level was observed in group II as compared with group I. Effect of Gabapentin, SA, SP and their combination with L-Arginine on SOD is significant increase in its level with $p<0.01$** compared to group II (Figure7).

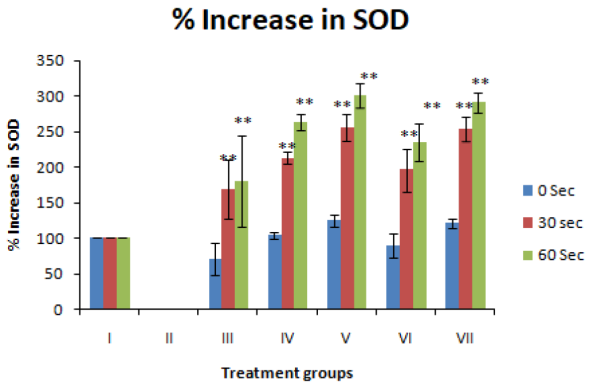

Figure 7: Percent increase in SOD antioxidant enzyme.

DISCUSSION

Neuropathic Pain (NP) is occurring due to neurodegeneration in central and peripheral nervous system.[16] The evaluation of neuropathic pain in humans is complex because most of the stimuli required to induce neuropathic pain produce irreversible damage. Therefore, there is a need of validated and easily reproducible animal models of neuropathic pain to evaluate the analgesic potential of novel pharmacotherapies for treating neuropathic pain. Different types of animal models have been established to meet the diverse etiology and consequently the diverse manifestations of neuropathy.[27] Currently, the protecting role of phenolic acids on neurons and glial cells has been interestingly considered and research on neuroprotection by phenolic acids has been successfully carried out and published.[28]

Cancer is a major contributor to the death rate worldwide. Currently, modern chemotherapy is emerging to treat various complicated malignancies, which is increasing the survival rate of cancer. But along

with this, these chemotherapeutic agents are resulting in many adverse effects.[29] Taxanes are a first-line group of antineoplastic drugs used to treat breast, lung, prostate and other gynaecological malignancies. Paclitaxel is a prototypic semisynthetic drug from taxane group, derived from the precursor 10-deacetylbaccatin III. This precursor is obtained from tree *Taxus baccata*. Peripheral neurotoxicity and myelosuppression are two major toxicities associated with use of paclitaxel.[30]

Mechanism of neuropathy induced by paclitaxel is thought to be dysfunctioning of microtubules in dorsal root ganglia, axons and Schwann cells. Paclitaxel forms abnormal microtubule bundles in the cytoplasm, which disrupts normal cell physiology and leads to cell proliferation. This impairs normal neuronal development and results in neuronal death.[31] Paclitaxel, if given intraperitoneally, can produce a dose-limiting painful peripheral neuropathy and can be used as an animal model to evaluate the effect of various drugs on neuropathic pain.[31] Low doses of paclitaxel lead to dysfunction of axons and Schwann cells and produce pain hypersensitivity including allodynia and hyperalgesia, characterized by numbness, paresthesia and a burning pain in the hands and feet.[32]

Chemotherapy is the main approach in cancer treatment, but side effects like peripheral neuropathy produced by chemotherapeutic drugs can limit treatment. Paclitaxel binds to microtubules and causes arrest of mitosis in cancer cells and also enhances neuronal excitation, followed by apoptotic cell death. Paclitaxel increases oxidative stress as well.[16] Paclitaxel induces neuronal biomarkers like activation of lipid peroxidation, and rise in inflammatory mediators. It reduces both paw retention time and maximum tolerant force. In pathological conditions, TRPA1 and TRPV4 are responsible for the activation of mechanical stimuli, nerve injury or neuropathic conditions. TRPA1 has been shown to be activated by oxidative stress leading to increased nerve fiber excitability and manifestation of mechanical and cold hypersensitivity behaviors in rodents. Administration of chemotherapeutic drug (e.g., paclitaxel) causes peripheral neuropathy in rodents, cold temperatures activate TRPA1 and TRPM8, due to hot condition/temperature leads to activation of TRPV1.[33] Neuroinflammation and the expression of pro-inflammatory cytokines (IL-1, IL-6, IL-8, IL-12, IL-18, IFN-y and TNF) are correlated to pain transmission and development of inflammatory and neuropathic pain. Activated glial cells (in the spinal cord) can release pro-inflammatory cytokines, which initiate a signal transduction cascade cause the release of excitatory amino acids and promote pain transmission.[34]

In a study of nimodipine in paclitaxel-induced peripheral neuropathy by Ciotu *et al*. (2016), the mechanical sensitivity was assessed using a Dynamic Plantar Aesthesiometer and an automated version of the von Frey filaments. They found that hyperalgesia induced by an antineoplastic drug (paclitaxel) reduces the time to response to mechanical stimuli. The results of this study underline a progressive increase in tactile pain sensitivity following paclitaxel administration.[35] Through another research, Griffiths *et al*. (2018) have studied evoked and ongoing pain-like behavior in a rat model of paclitaxel-induced peripheral neuropathy. In this study rats were administered with 2 mg/kg paclitaxel i.p. on four alternate days (0, 2, 4, and 6). They assessed mechanical hypersensitivity using von Frey filament test, cold hypersensitivity using acetone, heat hypersensitivity using a radiant heat source (infrared beam). They reported on day 14, statistically significant ($p<0.05$) mechanical and cold hypersensitivity started to emerge, which peaked by day 28.[15]

The present study has shown that repetitive administration of paclitaxel (2mg/kg, i.p.) significantly produced signs of neuropathic pain by accelerating thermal and mechanical hyperalgesia and allodynia. It also has produced motor in-coordination. The treatment with Syringic acid (25mg/kg), Sinapic acid (10mg/kg) and their combination with L-Arginine (50mg/kg) attenuated the paclitaxel-induced neuropathic pain in rats by improving its behaviour assessed by using Rota rod (motor coordination), hot plate method (thermal hyperalgesia), cold plate method (cold allodynia), and Von Frey filaments (mechanical hyperalgesia).

Oxidative stress plays a main role in the pathogenesis of neuropathic pain. Malondialdehyde (MDA) is a product of lipid peroxidation that is reactive to Thiobarbituric Acid (TBA). Lipid peroxidation is a free-radical-mediated chain of reactions that, once initiated, results in an oxidative deterioration of polyunsaturated lipids.[36]

Glutathione (GSH) is a tripeptide which is composed of the amino acid cysteine, glycine and glutamic acid and is also, the major antioxidant in the non-lipid portion of cells in most of the cytoplasm. Reduced Glutathione (GSH) is a highly copious cell compartments and also, a soluble antioxidant. GSH shows its antioxidant effects in several ways.[8]

In a study performed by Kaur and Muthuraman, in 2019, the intraperitoneal administration of paclitaxel (PT, 2 mg/kg) resulted in a significant ($p<0.05$) rise in lipid peroxidation products (TBARS) total calcium, TNF-α, superoxide anion and a decrease in GSH and SOD content as an indication of oxidative stress, inflammation and neuronal damage when compared to the control

group. Subsequent reaction of lipid peroxidation also altered cellular endogenous antioxidant substances i.e., GSH in paclitaxel-treated animals.[16]

In accordance with above-published research, in our study, we observed a decrease in MDA and an increase in GSH and Superoxide Dismutase (SOD) levels after treatment.

Paclitaxel increases neuronal free radical production. Abundant accumulation of cytosolic free radicals is known to activate lipid peroxidation of the neuronal membranes.[16] Reduction in MDA by these phenolic acids and its combination indicates reduced lipid peroxidation and attenuation of oxidative stress. Combination of L-Arginine have potentiated effect of single dose of respective phenolic acid and this result is suggesting that dose of phenolic acid can be reduced to get beneficial effects in therapy of neuropathic pain. Administration of L-Arginine has been shown to increase cerebral blood flow and reduce neurological damage. Thus, syringic acid and sinapic acid in combination with L-arginine treatment has shown a significant protective effect than a single drug therapy in paclitaxel-induced neuropathic pain and these benefits may be possibly due to its antioxidant, analgesic and neuroprotective effect. A combination of phenolic acids and amino acids may be helpful in the treatment of neuropathies with minimum dose requirements and adverse effects.

CONCLUSION

Syringic acid and sinapic acid are proven with antioxidant and neuroprotective effect, also used in the treatment of neuropathic pain. In the present study, combinational therapy of L-Arginine with syringic acid and sinapic acid has shown significant potentiation of individual effects of these phenolic acids through a reversal of behavioural changes and oxidative stress induced by paclitaxel. Potentiation of these effects by L-Arginine may be helpful for the dose reduction of these phenolic acids in the treatment of neuropathy. The results from the present study will be helpful for further research studies to be extended at biochemical, molecular and clinical levels.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING INFORMATION

There is no funding agency involved in current research.

ABBREVIATIONS

SA: Syringic acid; **SP:** Sinapic acid; **iNOS:** Inducible Nitric Oxide synthetase; **COX-2:** Cyclooxygenase 2; **MDA:** Malondialdehyde; **casp-3:** Caspase 3; **SOD:** Superoxide dismutase; **GSH:** Glutathione; **DTNB:** Dithiobis nitrobenzoic acid.

SUMMARY

Paclitaxel is taxane derivative used in lung and breast cancer treatment but associated with adverse effects like peripheral neuropathy and mylosupression. Microtuble disruption and oxidative stress is major mechanism behind its adverse effect, so antioxidants can be beneficial in treating its adverse effects. Phenolic acids i.e. Syringic acid and sinapic acid with potent antioxidant capacity are investigated in this research in combination with L-arginine. Combination has shown more potent effect than individual drug. Thus, this will be helpful for dose reduction of these phenolic acids in the treatment of neuropathy.

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