Evaluation of Syringic Acid and Sinapic Acid in Chronic Constriction Injury Induced Neuropathy

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Abstract

Objective: As oxidative stress is a key contributor in neuropathy, natural antioxidants may be helpful in its treatment. Syringic acid and Sinapic acid are polyphenols with proven antioxidant, anti-inflammatory activity. So, this study designed to evaluate effect of Syringic acid and Sinapic acid in chronic constriction injury (CCI) induced neuropathy.

Method: Wistar rats divided into ten groups. CCI surgery performed by method of Bennett and Xie and animals treated with Syringic acid 12.5, 25, 50 mg/kg/day, Sinapic acid 5, 10, 20 mg/kg/day and gabapentin 300 mg/kg/day orally for 5 weeks. Heat hyperalgesia, cold allodynia, mechanical allodynia and mechanical hyperalgesia assessed weekly. At the end of treatment motor nerve conduction velocity measured. Blood sample collected under light anaesthesia for biochemical and cytokines estimations (electrolytes, C-reactive proteins, TNF-α, IL-6) and sciatic nerve isolated after sacrifice for antioxidant (MDA, GSH, SOD, NO) and histological study.

Result: 5 weeks treatment with Syringic acid and Sinapic acid decreased allodynia and hyperalgesic response significantly with p < 0.01**. Nerve conduction velocity increased significantly in dose dependant manner (p < 0.05*, p < 0.01**). We found dose dependant and significant reversal of alterations in markers of oxidative stress, antioxidants, electrolytes and cytokines with p < 0.05* and p < 0.01**. Histopathological damage in neuronal tissue is protected by treatment with Syringic and Sinapic acid.

Conclusion: Syringic acid and Sinapic acid have shown neuroprotective effect which may be attributed to its anti-hyperalgesic, antioxidant and anti-inflammatory action.

Graphical Abstract

Keywords: Neuropathy; CCI; Phenolic Acids; MNCV; Neuroprotective

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Introduction

Neuropathic pain (NP) are the type of pain associated with dys-functioning of the nervous system or neuronal injury [1]. NP are also associated with damage to nerve due to tumours, diabetic neuropathy, herpes zoster, complex regional pain syndrome, AIDS, hypoxia etc [2]. These pain mainly disturbs quality of life of patients leading to depression and thus have significant impact on social status. It is reported that millions of American adults usually suffer from chronic pain and 17.9% suffer from neuropathic pain [3]. NP may be multifactorial resulting into neuronal impairment. The pathophysiology of pain is complex and involves central and peripheral pathways viz. neurotransmitter release, alteration in expression of ions and pain pathway [4]. It is known that both hyperalgesia and allodynia coexist in both, inflammatory and neuropathic pain [5]. Various metabolic disorders, inflammatory reactions, viral infection, direct neuronal trauma, neurological diseases, chronic disease like cancer or use of chemotherapeutic drug creates physiological stress and which further results into NP by damaging neurons and associated neuronal functional disabilities. Pain may be triggered by even any non-specific, small intensity stimulus, as neuronal injury changes neurophysiology to the long extent. Such neuronal changes lead to over-expression of neuronal receptors and ion channels. This may generate abnormal action potentials and such abnormalities synaptic transmission can result in neuropathic pain. Currently, this pathway is being targeted for drug discovery [6]. Abnormality in the electrophysiological measurements is observed in neuropathic pain due to axonal damage and demyelination [7].

It is well proven that oxidative stress contributes significantly in etio-pathogenesis of NP [8]. The mechanism of nerve dysfunctions induced by oxidative stress include generation of reactive oxygen species (ROS), reactive nitrogen species (RNS), lipid peroxidation, DNA damage and decrease in endogenous antioxidants. These actions result in axonal damage and microvasculature disruption in the peripheral nervous system [9]. Secondary plant metabolites e.g. different phenolic acids have been proven effective in the prevention and treatment of various diseases. Many researchers have studied and proven free radical scavenging and antioxidant activity of phenolic acids. Protective action of phenolic acids on glial cells and neurons is recently focused for further research to explore neuroprotective role of phenolic acids. In future, neurological treatment may be combined with phenolic acids as promising approach because of abundant availability, high stability, high oral absorption and efficient brain absorption of many phenolic acids [10]. Isolated plant chemical constituents are proven as good free radical scavengers, which have key role in improvement in neuropathic symptoms [11].

Syringic acid (SY) is a phenolic acid in plants synthesized by shikimic acid pathway. It is found in different fruits and vegetables. SY has various therapeutic uses like in prevention of diabetes, cardiovascular diseases, cancer, cerebral ischemia. It possesses strong anti-oxidant activity which is responsible for its beneficial effects i.e. antimicrobial, anti-inflammatory, antiendotoxic, neuro and hepatoprotective activities [13].

Sinapic acid (SP) is found in various spices, citrus fruits, berries and vegetables. It is widely used in cosmetic industry due to its strong antioxidant, antimicrobial, preservative and anti-inflammatory activity [14]. It may be beneficial in the treatment of Alzheimer’s disease, because it prevents memory loss and reduces oxidative stress [15].

Although various animal models are available to study neuropathy, sciatic nerve compression is focused to induce peripheral nerve injury. The sciatic nerve ligation is comparatively easy surgery and it allows tests for paw withdrawal reflexes [16].

So, the present study is undertaken to evaluate effect of SY and SP in CCI induced neuropathy.

Materials and Methods

Syringic acid and sinapic acid purchased from sigma Aldrich, USA. Ketamine (Ketamax 50) from Troikaa Pharmaceuticals, India, Xylazine (Xylaxin) from Indian Immunologicals Ltd. India and Oxytetracycline ((Terramycin) Pfizer, India. Standard drug gabapentin supplied by Sun Pharma, India.

Research proposal prepared as per guidelines of CPCSEA and approved by Institutional Animal Ethical Committee (IAEC) of SNJB’s SSDJ College of Pharmacy, Chandwad, India (CPCSEA approval letter No. SSDJ/IAEC/2018/01).

Acute oral toxicity study conducted as per OECD guidelines 425, Up and Down procedure [17]. No any death observed after administration of oral dose of 2000mg/kg 5 female rats. So LD50 is concluded more than 2000mg/kg. From the literature survey, minimum

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therapeutic doses of Syringic acid finalised as 12.5, 25, 50 mg/kg/day and of Sinapic acid as 5, 10, 20 mg/kg/day orally. Standard drug gabapentin 300 mg/kg/day p.o. used to compare the results.

Animals used were Wistar rats of either sex and divided into 10 groups (n = 6) and treated for 5 weeks as follows:

1. Negative Control: Received vehicle only.
2. Positive Control: Chronic Constriction Injury (CCI).
4. SY1: CCI + Syringic acid 12.5 mg/kg/day p.o.
5. SY2: CCI + Syringic acid 25 mg/kg/day p.o.
6. SY3: CCI + Syringic acid 50 mg/kg/day p.o.
7. SP1: CCI + Sinapic acid 5 mg/kg/day p.o.
8. SP2: CCI + Sinapic acid 10 mg/kg/day p.o.
9. SP3: CCI + Sinapic acid 20 mg/kg/day p.o.
10. Std: CCI + Gabapentin 300 mg/kg/day p.o.

**Induction of neuropathy by chronic constriction injury**

Animal anesthetized by using mixture of ketamine and xylazine (90 mg/kg, i.p and 5 mg/kg, i.p, respectively). Hair around the mid-thigh shaved. The common sciatic nerve of the right hind exposed at the level of the middle of thigh by blunt dissection through biceps femoris. The exposed sciatic nerve tied with ligature (4.0 silk chromic gut ligature) around it with about 1 mm spacing long. After ligation, muscles and skin sutured separately. Povidone iodine solution applied externally by cotton swab and oxytetracycline 25 mg/kg, i.m. injected for next 3 days. The operated animals caged individually and feed and water provided ad-libitum [18].

**Behavioral study:** Peripheral nerve injury in diabetic neuropathy is characterized by behavioral biomarkers such as dysesthesia, hyperalgesia, allodynia and with motor in co-ordination [19].

**Mechanical allodynia (Von Frey test):** Individually, rat placed on elevated maze in acrylic cage and adopted for test environment for at least 15 minutes. From below the mesh floor, Von Frey filament applied to the planter aspect of right hind paw. Enough force of filament applied against paw (causing slight bending) and hold for sec. Withdrawal of paw considered as a positive response [12]. Observations of mechanical allodynia noted with 6 repeated application of varying force of Von Frey filament. Observations recorded in the format of OXXOXO, where O indicated- no withdrawal response and X indicates withdrawal response. This used method of observation is up and down method of Dixon and 50% gm threshold calculated by formula:

$$50\% \text{ g threshold} = \left(10 \times \frac{E(x+f+k\delta)}{10,000}\right)$$

Where $Xf$ is log units of the last von Frey filament used; $k$ is a tabular value for the pattern of positive/negative responses; and $\delta$ is a mean difference (in log units) between stimuli (here, 0.224) [32].

**Cold allodynia (Cold plate test):** Here, the animal placed on the cooled plate at 5°C and the time to induce nociceptive behaviour indicated by shivering and paw licking recorded as the response time [20].

**Mechanical hyperalgesia (Randall sellitto method):** Randall Selitto test is commonly used for testing acute mechanical sensitivity, measured by paw withdrawal threshold. Through the dome-shaped plastic tip of this apparatus, steadily increasing pressure applied on dorsal surface of the rat’s hind paw. The withdrawal threshold (in % CBK) for each paw recorded. Measurements repeated 2 or 3 times on each paw [21]. Animal gently hold to immobilize it and its paw placed on the apparatus and the tip of device allowed to apply on paw with application of increasing mechanical force and withdrawal latency to the pressure supported was noted down [22].

**Heat hyperalgesia (Hot plate test):** Eddy’s hot-plate used to study the thermal nociceptive threshold by keeping the temperature at 55 ± 2°C. Animal individually tested by placing on the hot plate and paw licking latency (sec) recorded. Test cut-off time of 20 seconds was maintained [23].

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**Evaluation of motor nerve conduction velocity (MNCV):** MNCV recording carried out at the end of treatment. Animals anesthetized by Ketamine (90 mg/kg i.p) and Xylazine (5 mg/kg i.p). MNCV assessed by using 8 channel powerlab (AD Instruments) with animal nerve stimulating electrode (MLA0320) and needle electrodes (MLA1204). Action Potential generated by applying stimulating electrode at proximal end and recording done from distal end. (PowerLab setup as frequency: 10Hz, duration: 0.1ms, amplitude: 4V). The distance between the stimulating electrode and recording electrodes divided by latent period is calculated as conduction velocity. Latent period considered as the time between applications of stimulus until the peak of the action potential [24].

On next day, before scarification, blood collected by retro-orbital method under light anaesthesia. Serum and plasma separated for electrolyte and cytokine estimation.

**Antioxidant study**

a) **Preparation of tissue homogenate:** After scarification, isolated sciatic nerve homogenized in ice cold Tris HCl buffer (10 mM, 10% w/v). Centrifugation (using Remi C-24 high speed cooling centrifuge) carried out at 10,000 rpm for 15 minutes. Clear supernatant used for further estimations [25].

b) **RGSH (Reduced glutathione):** It is determined by DTNB reagent method. The colour intensity developed measured at 412 nm against reagent blank [26].

c) **Superoxide dismutase (SOD):** The superoxide dismutase activity is determined by the method described by Misra and Fridovich. The absorbance of formed adenochrome complex measured at 480 nm [27].

d) **Nitric oxide (NO):** The nitrite level is estimated using method of Guevara with Griess reagent. Absorbance read at 540 nm against Griess reagent as a blank [28].

**Oxidative stress determination: MDA (Malondialdehyde):** It is determined by TBARS method. Absorbance of organic phase recorded at 535 nm [29].

**C-reactive protein (CRP):** It is determined by immuno-enzymatic method.

**Serum electrolytes:** Serum sodium (Na⁺) and potassium (K⁺) levels (mmol/L) are determined by direct ion selective electrode method.

**TNF-α, IL-6:** It is estimated by MACSPlex cytokine 12 kit, developed for the simultaneous flow Cytometric detection of cytokines.

**Histopathology:** Isolated sciatic nerve kept in the 10% formalin and sent for study [34].

**Biostatistics**

All data expressed as mean ± S.D (n = 6). Statistical analysis performed using Graph Pad Prism Software. For multiple comparisons, one-way analysis of variance (ANOVA) used followed by with Dunnet test. # indicates significant difference compared to negative control group. p < 0.05* and p < 0.01** considered statistically significant and a is statistically non-significant as compared to positive control group.

**Results and Discussion**

Preclinical model of neuropathic pain (NP) requires specific model to induce chronic pain. Metabolic models anti-cancer drug induced pharmacological models and traumatic (surgery) models are available animal models for NP. CCI is well established model for neuropathy. Loose or tight ligations of the sciatic nerve produces long lasting hyperalgesia and allodynia in animal models of neuropathic pain. CCI model has previously used to understand the mechanism of peripheral neuropathic pain [30].

**Behavioral study**

**Mechanical allodynia (Von Frey test):** Allodynia term refers to pain due to normally non noxious stimuli. In animal models of neuropathy, nociceptive behaviour can be provoked by minimum force of Von Frey filaments to the paw (maximum up-to 15g). Nitrosative stress, polymerase activation, increased excitability of ganglion neurons are factors thought to be associated with allodynia [31].

It is observed in positive control group that allodynia produced from 1st week indicated by withdrawal response to minimum force of filament. In control animals, 50% gm threshold decreased significantly (p < 0.0001****) compared to normal animals. Treatment with SY
and SP has shown to increase the threshold and force giving withdrawal response is found to be increased in dose dependent manner (p < 0.001**) with change in observation format (Figure 1).

![Figure 1: 50% gm threshold by Von Frey filament test in CCI induced neuropathy.](image1)

# is p < 0.0001 compared to normal group. ** is p < 0.001 and *** is p < 0.0001 compared to control group.

**Cold alldynia (Cold plate test):** Time of onset of shivering from cold plate (5°C) is found to be decreased in control group than normal group. Symptoms of cold alldynia observed from 1st week of surgery. Sham control group showed decrease in shivering onset compared to normal but statistically non-significant. In SY and SP decreased cold alldynia in dose dependent manner. These test drugs have shown protective effect from 1st week of treatment and 5 weeks treatment shown statistically significant protection of cold alldynia with p < 0.05*. SY 3 and std drug (Gabapentin) shown it with p < 0.01** (Figure 2).

![Figure 2: Onset of shivering response (in sec.) in cold plate test.](image2)

# is p < 0.001 compared to normal group. a is non-significant compared to normal, ** is p < 0.001 and *** is p < 0.0001 compared to control group.

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The shivering and paw withdrawal response observed on the cold plate may be mediated by various factors. Cold stimuli activate neuronal Na+ channels and causes release of neurotransmitters mediated through pre-synaptic Ca++ channels. These ion channels are specifically localized on small, un-myelinated C-fibres and activation of these channels release neuropeptides, such as substance P and calcitonin gene related peptide from C-fibres. Thus, in CCI model, allodynia is produced through C-fibres and skin cooling activates thermoreceptors expressed in Ad fibres [33]. This cold allodynia was found to be attenuated with SY and SP treatment in dose dependant manner.

**Mechanical hyperalgesia (Randall Selitto test):** Withdrawal threshold of paw pressure is measured in terms of % CBK by Randall-Selitto apparatus. % CBK is found to be decreased in positive control group from 1st week of CCI indicating decreased paw withdrawal threshold. 5 weeks treatment with SY and SP has shown statistically significant (p < 0.01**) protective effect indicted by significant increase in %CBK. All observations compared with positive control and standard gabapentin (Figure 3). The withdrawal threshold after mechanical pressure was considered to be associated with oxidative stress [31].

**Heat hyperalgesia (Hot plate test):** Paw withdrawal latency and jumping response observed after placing animal on preheated plate (55°C). Thermal hyperalgesia is found to be produced in positive control group from 1st week of CCI. Sham control group has also shown significant decrease in paw withdrawal latency compared to negative control animals. Thermal hyperalgesia is found to be prevented from 1st week. After 5 weeks, treatment with SY and SP has shown statistically significant protection (p < 0.01**) of thermal hyperalgesia (Figure 4).
Motor nerve conduction velocity (MNCV): At the end of 5th week, nerve conduction velocity (m/sec) was measured. Positive control animals have shown marked reduction in conduction velocity compared to negative control animals. This indicates neuronal damage protected in treatment groups. Sham control animals have shown significant decrease in MNCV compared to negative control. Lower dose SY1, has increased conduction velocity but statistically non-significant. Treatment with SY and SP has prevented this damage and shown to increase conduction velocity statistically significant (p < 0.05*) than positive control group and gabapentin have improved it with significance p < 0.01** (Figure 5).

Abnormalities in motor nerve conduction may be due to blood flow reduction induced by ligative injury and such resultant endoneural hypoxia which lead to development of neuropathy [34]. This neuronal hypoxia may be normalised by SY and SP which was thought to increase conduction velocity.

Oxidative stress (MDA): Estimation of lipid peroxidation done by measuring the levels of malondialdehyde (MDA) which is direct indicative of oxidative stress. MDA measured from sciatic nerve tissue homogenate and absorbance recorded at 535 nm. Oxidative stress and lipid peroxidation are found to be increased in positive control group indicated by increased absorbance. This MDA absorbance of positive control was considered as 100% (i.e. 0% inhibition of MDA) and comparatively % inhibition calculated for test and standard groups. Absorbance is comparatively decreased and % inhibition is increased significantly (p < 0.05*) in test groups in dose dependent manner and in standard group with p < 0.01**. SY1 has shown statistically non-significant decrease in MDA. This indicated that SY and SP are able to reduce lipid peroxidation and oxidative stress generated by CCI (Figure 6).

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Antioxidants

Glutathione (GSH): It is antioxidant, abundantly available in cell, its deficiency and impaired synthesis occurs in neuropathy [11]. After CCI, GSH level decreased in positive control group indicated by significant decrease in absorbance at 412 nm. This absorbance increased in treatment groups dose dependently. % increase in GSH level calculated by considering 100% GSH level of negative control and 0% in positive control group. This study indicated 5week treatment with SY and SP (SY3, SP2, SP3 with p < 0.05*) is able to increase antioxidant GSH level in cell (Figure 7). A dose of SY1 and SY2 and SP1 increased GSH level but statistically non-significant. Gabapentin improved GSH with p < 0.001**. Glutathione, a tripeptide which is composed of the amino acids cysteine, glycine and glutamic acid and also, the major antioxidant in the non-lipid portion of cells in most of the cytoplasm. It exists in a reduced form (GSH) and an oxidized form (GSSG). In addition to neutralize free radicals, glutathione is responsible for maintaining the antioxidant activity of other antioxidants, stabilizing its reduced form [27].

Figure 7: % increase in GSH level after treatment of test drugs.

Superoxide dismutase (SOD): SOD catalyzes the dismutation of superoxide into oxygen and hydrogen peroxide. Antioxidant agents like Catalase, Superoxide Dismutase and Glutathione etc. are helpful for treatment and prevention of various diseases. A dismutase is an enzyme that catalyse the reaction of two identical molecules to produce molecules in different oxidative states. In the absence of SOD, two superoxide ions can spontaneously dismutate to produce hydrogen peroxide and singlet oxygen. SOD catalyses a reaction between two superoxide ions to produce hydrogen peroxide and triplet oxygen [27]. CCI shown to decrease level of SOD in positive control group compared to negative control animals, but 5 weeks treatment with SY and SP increased antioxidant capacity by increasing SOD level (Figure 8) in dose dependant manner (p < 0.01** and SP1 with p < 0.05*).

Figure 8: % increase in SOD level after treatment with test drugs.
Nitric oxide (NO): The production of NO in the brain may occur due to oxidative stress and it can be determined by estimation of nitrite level. Nitric oxide has been involved in the cytotoxicity by activation of macrophages or excess stimulation of neurons by glutamate [35]. As nitric oxide synthase (NOS) activity is upregulated in CCI rats, there is enhanced production of NO, which is metabolised to nitrate and nitrite. Estimation of nitrate and nitrite is thus, convenient and simple way to determine NOS activity [8]. In this study CCI has increased NO production in positive control group, indicated by increased absorbance. By considering positive control absorbance as 100% (i.e. 0% inhibition), NO inhibition calculated in treatment group. SY1 and SP2 shown increase in % inhibition with $p < 0.05^*$, SP1 shown statistically non-significant and other treatment groups improved it with $p < 0.01^{**}$ (Figure 9). Thus, SY and SP are phenolic acids found to decrease oxidative stress and increased antioxidant enzymes in CCI induced neuropathy.

C-reactive proteins (CRP): CRP is a key inflammatory factor that is regulated by IL-6, IL-1 and TNF-α, and produced by the liver in response to inflammation [36]. It is found that serum CRP is increased in positive control group compared to negative control group indicating possibility of neuronal damage and neuroinflammation. Sham control group shown minimum changes in CRP compared to negative control. 5 weeks treatment with gabapentin ($p < 0.01^{**}$), SY (SY1 with $p < 0.05^*$ and SY2, SY3 with $p < 0.01^{**}$) and SP (SP1 with $p < 0.05^*$ and SP2, SP3 with $p < 0.01^{**}$) has shown protective effect indicated by decrease in CRP compared to positive control group (Figure 10).
**Serum electrolytes:** Serum Na⁺ and Cl⁻ level is found to be decreased and K⁺ level increased in positive control animals compared to negative control animals (Figure 11). 5 weeks treatment with SY and SP have reversed the effect by increasing serum Na⁺, Cl⁻ (p < 0.05*) and decreasing K⁺ level (p < 0.05*) indicating its neuronal protective effect in dose dependant manner. SY1 and SP1 decreased K⁺ level but statistically non-significant.

![Serum Sodium and Chloride (mmol/L)](image1)

*Figure 11: Serum electrolytes (mmol/L) in CCI and treated groups.*

**TNF-α and interleukin-6:** All types of central and peripheral neural lesions, whether ischemic, traumatic, infectious, or immune mediated initiates inflammatory reactions to release proinflammatory mediators i.e. cytokines and IL-6, and TNF-α [37].

CCI had significantly increased IL-6 and TNF-α as compared to negative control rats (Figure 12). Sham surgery group animals have shown non-significant increase IL-6 but statistically significant increase in TNF-α compared to normal negative control animals. Gabapentin, SY and SP treated animals have shown significant decrease in IL-6 and TNF-α (p < 0.05*). The observed increase in inflammatory cells infiltration and changes in cytokines levels confirm inflammatory pathology [37]. Oxidative stress causes production of abnormal cytokine production (TNF-α and IL-6) [36]. Immune system activation has been shown to facilitate and increase neuropathic pain. A number of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6 and IL-17, have been found to be elevated in animal models of neuropathic pain [38]. Treatment with SY and SP has shown to reduce neuroinflammation indicated by significant decrease in these cytokines.

**Histopathology:**

Histopathology Section of H and E stained sciatic nerve of CCI control rats showed epineuronaloedema and infiltration of neutrophils around blood vessels and swelling of nerve fibers (100x) compared to negative control group (Figure 13). Treatment with SY and SP and Gabapentin showed mild oedema and few infiltrating neutrophils around blood vessels and minor swelling of nerve fibres.

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Conclusion

In the present study, CCI have induced neuropathy symptoms within 1 week post-surgery in positive control group. 5 weeks treatment with SY and SP has found to protect behavioural changes by reducing mechanical allodynia, thermal hyperalgesia and mechanical hyperalgesia. Oxidative stress and antioxidants enzyme level in also found to be protected in treated groups in dose dependant manner. Nerve conduction velocity was decreased in positive control group due to neuronal hypoxia produced after ligation. This was significantly

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improved by treatment with SY and SP. Markers of neuroinflammation i.e. C reactive protein, Interleukin-6 and TNF-α were found to be increased in positive control group after CCI surgery. These cytokine levels were found to be decreased in treatment group of SY and SP. Thus, from this result, it is concluded that Syringic acid and Sinapic acid have neuroprotective role which may be attributed to their anti-hyperalgesic, antioxidant and anti-inflammatory action. So, these natural phenolic acids syringic acid and Sinapic acid can be therapeutically used in combination with current treatment of neuropathy.

Bibliography


