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Syringaldehyde Attenuates Chronic Constriction Injury-Induced Neuropathic Pain In Sprague-Dawley Rats Via PGE2-iNOS Inhibition

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Abstract
Neuropathic pain is a one of the most unbearable pain condition severely affecting day-to-day life in affected patients. Syringaldehyde is a compound isolated from various plant species. Syringaldehyde has shown several pharmacological properties including anti-inflammatory, anti-oxidant activities. In this work, to assess in-vivo pharmacological effect of Syringaldehyde in development and maintainace of neuropathic pain, male SD rats were subjected to CCI ligation surgery of sciatic nerve with assessment of mechanical allodynia using von Frey filaments and cold allodynia using acetone test from post-surgery day 3 onwards. CCI rats were given Syringaldehyde orally from day 7 to 14 and pain responses were recorded on day 7, 14. At the end of study, expression levels of PGE2 and iNOS mRNA was assessed in sciatic nerve of CCI rats. CCI surgery in rats developed mechanical and cold allodynia from post-surgery day 3 onwards with peak allodynia observed at day 7, and allodynia was maintained till day 14. Treatment with Syringaldehyde for from day 7 to day 14 showed reversal of mechanical and cold allodynia inhibition of CCI rats when allodynia was assessed on day 7 and day 14. Moreover, treatment with Syringaldehyde decreased mRNA expression levels of PGE2 and iNOS in sciatic nerve. The results from this study demonstrated the analgesic potential of Syringaldehyde in neuropathic pain induced by CCI surgery which may be mediated via inhibition of PGE2 and iNOS.

Keywords: CCI, Syringaldehyde, PGE2, iNOS, Allodynia, Neuropathic pain

Introduction

Neuropathic pain affects peripheral or central nervous systems and is a chronic, debilitating pain condition (Singh et al., 2017, Bernetti et al., 2021, Kaur et al., 2016). Nerve injury may occur as a result of various conditions like trauma, infection, inflammation, tumors, metabolic or endocrine diseases (Baron, 2006). Nerve injury causes inflammation at site of injury, activates nociceptors (De Jongh et al., 2003) which develops hyperalgesia (increased pain sensitivity to noxious stimuli) or allodynia (pain sensitivity to non-noxious stimuli) (Zanjani et al., 2006; Kaur et al., 2016).The available treatments for chronic neuropathic pain have limited efficacy in most patients (Finnerup et al., 2010). Thus, there is an unmet need to discover better therapies for management of neuropathic pain. Presently, treatment of neuropathic pain in patients include use of antiepilpetics, SSRI inhibitors, sodium and calcium channel blockers, NMDA antagonists; however utility of these treatment options is limited due to CNS adverse effects (Xu et al., 2012). Thus, management of neuropathic pain therapy remains an unmet medical need and it is necessary to focus on discovery of new therapeutic options for treatment of pain.

Plant derived phytochemical compounds are potential candidates for discovery of novel compounds for treatment of pain (Kumar et al., 2015). Syringaldehyde is a natural flavonoid isolated from various plants like Magnolia officinalis (Shen et al., 2009). There are different pharmacological properties exhibited by Syringaldehyde including anti-inflammatory, anti-oxidant, cardioprotective, neuroprotective and anti-diabetic activity (Stanikunaite et al., 2009; Bozkurt et al., 2014; Wu et al., 2022). Thus, Syringaldehyde can be potential therapeutic option in the treatment of neuropathic pain.

The present study aimed to ascertain pharmacological activity of Syringaldehyde in rat model of chronic constriction injury (CCI) induced neuropathic pain. To assess influence of biomarker in neuropathic pain, expression levels of pain biomarker was measured in sciatic nerve of rats with CCI injury.

Material and methods

Animals

Animal house of Dayananda Sagar University (Bengaluru, India) supplied adult male Sprague-Dawley rats (180- 200 g, 7-8 weeks old). All animals were maintained under controlled conditions like 12-h light-dark cycle and free access to food, water. Before experimental activity, animals were acclimatized to laboratory conditions for one week. Dayananda Sagar University's Institutional Animal Ethics Committee (IAEC) approved the experimental methods and procedures in animals.

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Compounds and treatment
Syringaldehyde and Gabapentin were procured from Sigma (Sigma, India). Syringaldehyde (5, 15, 50 mg/kg, po) and Gabapentin were given orally to rats in neuropathic pain model of CCI.
CCI surgery for induction of neuropathic pain in rats
Neuropathic pain was induced by CCI surgery of sciatic nerve as per procedure described earlier (Bennett and Xie, 1988). Rats were anesthetized with ketamine:xylazine mixture (80:10 mg/kg, i.p.), an incicsion was given near left thigh region, bluntly dissected biceps femoris muscle to expose left sciatic nerve. Sciatic nerve was separated from connective tissue and ligated with 4 loose knots using 4-0 chromic gut sutures. The overlying muscle and skin wound was closed using silk suture 3-0.

Recording Mechanical allodynia
A set of 8 von Frey filaments (Bioseb) ranging from 0.4 g to 15 g was used to measure mechanical paw withdrawal threshold (PWT) in rats by up-down technique (Chaplan et al., 1994). Baseline PWT was measured before CCI surgery and development of allodynia was assessed by measuring PWT on day 3, 6 post surgery. On day 7, rats with mechanical allodynia were divided into 5 groups; vehicle control, Syringaldehyde (5, 15, 50 mg/kg) and Gabapentin (100 mg/kg). Treatment was given for 8 days from day 7 to day 14 surgery and effect of treatment was assessed by recording PWT on day 7 and day 14 at 1 h post treatment. Effect of compounds was ascertained by calculating percentage maximum possible effect (%MPE) using formula:
%MPE= (post-treatment PWT – vehicle PWT)/(15 - vehicle PWT) x 100

Recording Cold allodynia (Acetone test)
The acetone test for recording cold allodynia was done following procedure described earlier (Choi et al., 1994). Briefly, rats were acclimated to test environment on wire mesh floor and acetone bubble was applied to the plantar surface of the hind paw. Paw withdrawal latency (PWL) for response (flinching of hindpaw) was recorded till 30 seconds following acetone application. Baseline PWL was measured before CCI surgery and development of allodynia was assessed by measuring PWL on day 3, 6 post surgery. On day 7, rats were divided into 5 groups; vehicle control, Syringaldehyde (5, 15, 50 mg/kg) and Gabapentin (100 mg/kg). One-hour after oral administration, effect of treatment was assessed by recording PWL. Treatment was continued for 8 days till day 14 surgery and effect of treatment was assessed by recording PWL on day 10 and day 14. Effect of compounds was ascertained by calculating percentage maximum possible effect (%MPE) using formula:
%MPE= (post-treatment PWL – vehicle PWL)/(30 - vehicle PWL) x 100

mRNA analysis
PGE2 and iNOS mRNA expression levels were measured in CCI operated sciatic nerve samples using reverse transcription quantitative polymerase chain reaction (RT-PCR) assay. After recording of PWL/ PWT, animals were sacrificed and ipsilateral (left CCI operated) sciatic nerve samples were collected to assess mRNA expression. Contralateral (right CCI non-operated) sciatic nerve samples from vehicle group were collected and used as normal control sciatic nerve. Sciatic nerve samples were homegenised, total RNA was extracted using RNA extraction kit (Krishgen Biosystems). After measuring RNA concentration and purity, isolated RNA was reverse transcribed into single stranded cDNA using iScript cDNA synthesis kit (Bio-Rad). RT-PCR was performed with SYBR green (Bio-Rad) using RT-PCR detection system (Applied Biosystems). Primers used for gene expression are mentioned in Table 1. Gene expression levels of pain mediators in test samples was normalized with GAPDH (housekeeping gene) and relative fold over gene expression was calculated as -
Relative expression= 2^-(Ct GAPDH – Ct target gene)

Table 1. List of primers

Gene	Primer sequence
GAPDH	F- 5'- ATGCTGGTGCTGAGTATGTC -3' & R- 5'- AGTTGTCATATTTCTCGTGGGTT -3'
PGE2	F- 5'- CCCACTCACCTGCTGCTACTC-3' & R- 5'- AGAAGTGCTTGAGGTGGTTGTG-3'
iNOS	F- 5'- CGAAACGCTTCACTTCCAA -3' &R- 5'- TGAGCCTATATTGCTGTGGCT -3'

Statistical analysis
To analyse statistical outcomes of study, 2-way analysis of variance (ANOVA) was performed with Bonferroni post-test and 1-way ANOVA was performed with Dunnett's post-test as specified in data.

Results
Induction of allodynia post surgery
Prior to CCI surgery, baseline PWT and PWL were recorded in rats and rats were subjected to CCI surgery. Development of mechanical allodynia was seen from day 3 onwards, as PWT of rats decreased from 11.4 g to 1.9 g on day 3. Mechanical

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allodynia was maintained till day 14. Similarly, in response to CCI surgery, cold allodynia was seen as PWL of rats decreased from 29.9 seconds to 7.8 seconds on day 3. As seen in mechanical allodynia, cold allodynia was also maintained till day 14 post surgery (table 2).

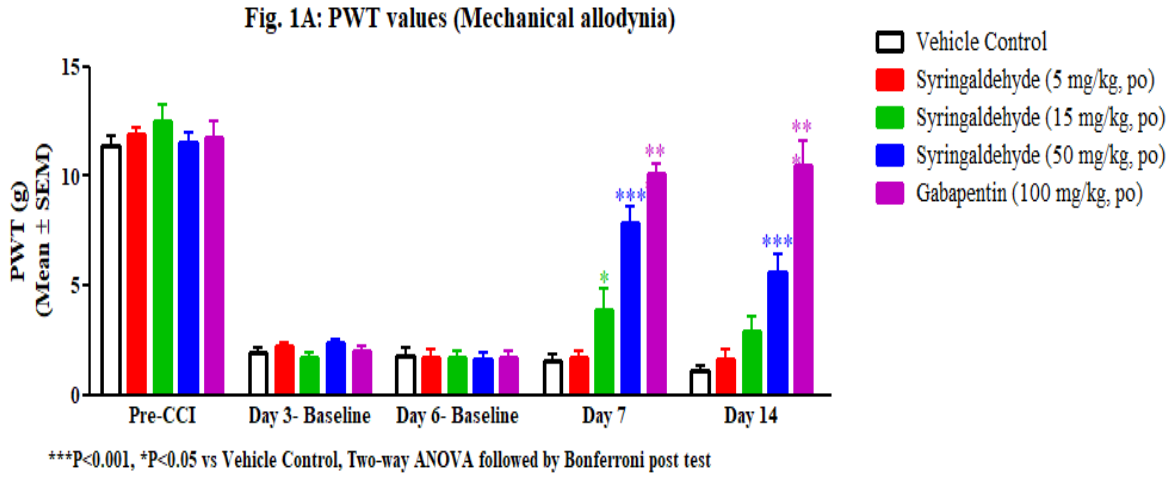
Table 2. Induction of mechanical and cold allodynia

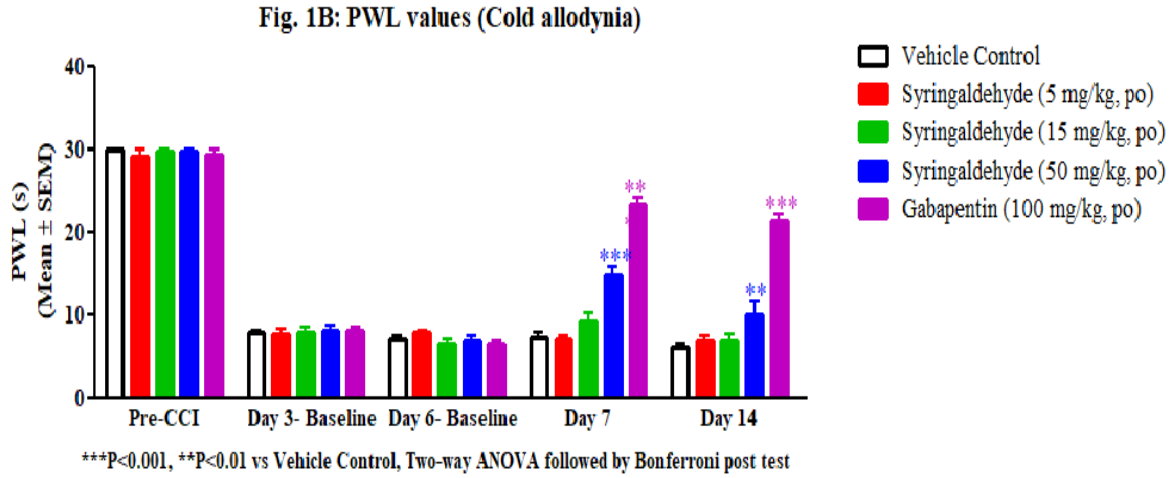
Allodynia	Surgery day				
	Pre-CCI	Day 3	Day 6	Day 7	Day 14
Mechanical allodynia (PWT in grams)	11.4	1.9	1.8	1.6	1.1
Cold allodynia (PWL in seconds)	29.9	7.8	7.1	7.4	6.2

Effect of Syringaldehyde treatment on CCI induced mechanical and cold allodynia

Post recording of baseline PWT and PWL on day 6, rats were randomized into 5 groups as per day 6 baseline mechanical allodynia. On day 7, rats were treated with vehicle/ Syringaldehyde/ Gabapentin and response was recorded at 1 h post treatment. Syringaldehyde treatment increased PWT (figure 1A) and PWL (figure 1B). Significant analgesic effect in terms of %MPE was seen with Syringaldehyde at dose of 15 mg/kg ($P<0.05$) and 50 mg/kg ($P<0.001$) for mechanical allodynia (figure 2A), while for cold allodynia 50 mg/kg dose showed significant analgesic effect ($P<0.001$, figure 2B). As expected, positive control Gabapentin showed significant analgesic effect for mechanical and cold allodynia ($P<0.001$). Treatment with Syringaldehyde was continued till day 14, and effect of treatment was assessed on day 14 at 1 h post treatment. Significant analgesic effect in terms of %MPE was seen with Syringaldehyde at dose 50 mg/kg for mechanical ($P<0.001$, figure 2A) as well as cold allodynia ($P<0.01$, figure 2B). As expected, positive control Gabapentin showed significant analgesic effect for mechanical and cold allodynia ($P<0.001$).

Figure 1. Effect of Syringaldehyde on CCI induced neuropathic pain. Paw withdrawal threshold (PWT) and paw withdrawal latency (PWL) values are expressed in as Mean ± SEM





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http://www.veterinaria.org
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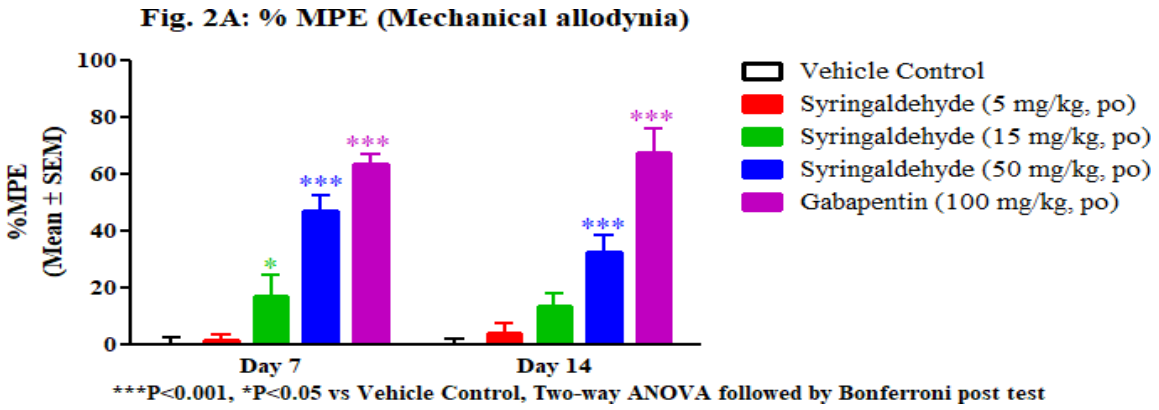
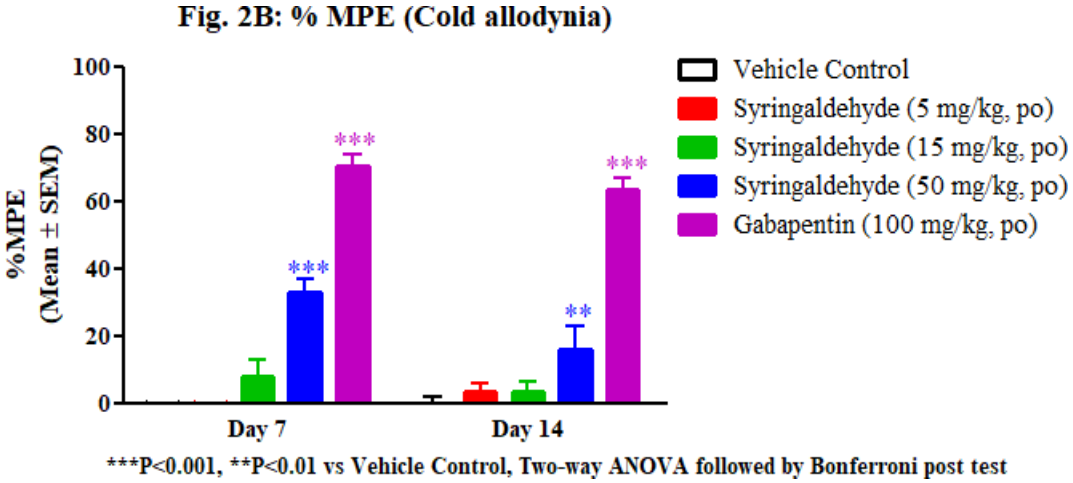
Figure 2. Effect of Syringaldehyde on CCI induced neuropathic pain. % MPE values are expressed in as Mean ± SEM





Effect of Syringaldehyde treatment on CCI induced biomarker expression levels

CCI surgery increased mRNA expression of PGE2 (11.03 fold, P<0.01, fig. 3A) and iNOS (12.97 fold, P<0.05, fig. 3B) in ipsilateral hind paw as compared to contralateral hind paw. Treatment with Syringaldehyde (5, 15, 50 mg/kg) decreased PGE2 mRNA levels (9.01, 5.40, 2.43 fold respectively, fig. 3A) and iNOS mRNA levels (10.17, 6.96 and 2.92 fold respectively, fig. 3B) with 50 mg/kg dose showing statistically significant reversal of PGE2 mRNA (P<0.01) and iNOS mRNA (P<0.05).

Figure 3. Effect of Syringaldehyde on CCI induced neuropathic pain. Gene expression fold over vs GAPDH values are expressed in as Mean ± SEM

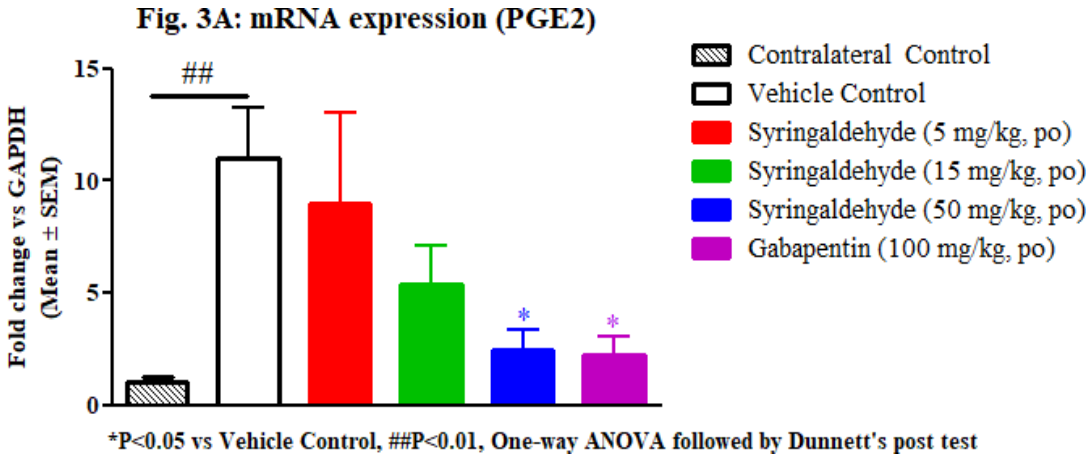


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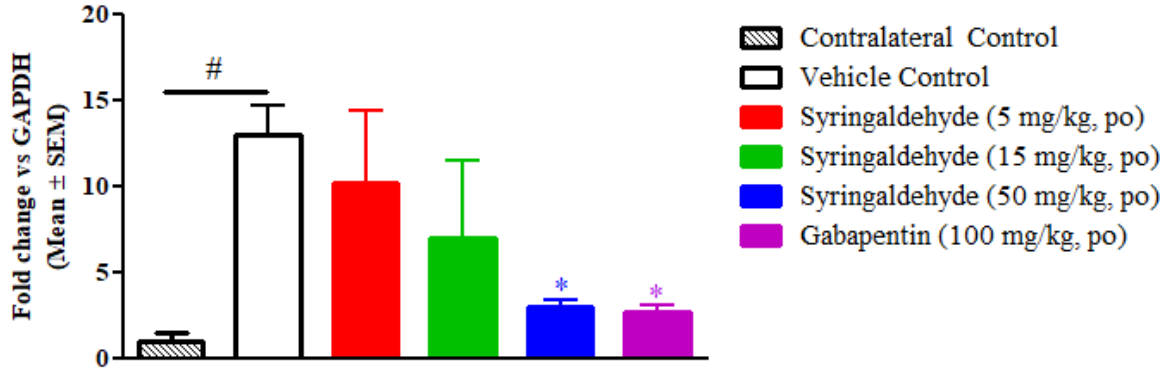
Fig. 3B: mRNA expression (iNOS)



***P<0.05 vs Vehicle Control, #P<0.05, One-way ANOVA followed by Dunnett's post test**

Discussion

CCI induced neuropathic pain is the most a widely used animal model to study mechanisms of neuropathic pain and CCI surgery model mimic pathophysiology of complex regional pain syndrome in humans (Bennet and Xie 1988, Jin et al., 2008). Sciatic nerve injury leads to local nerve inflammation, alters nerve structure and function which causes increase in pain sensitivity (Jaggi and Singh, 2010). CCI surgery causes an injury to the sensory afferents nerve fibers and develops long-term allodynia post-surgery (Bennet and Xie 1988, Austin et al., 2012). Nociceptors innervated with C fibres and thinly myelinated Ad fibres are physiologically involved in pain signalling. However, nerve injury results in phenotypic switch where involvement of Aß fibers in pain signalling leads to increased pain sensitivity and allodynia (Basbaum and Fields, 1984; Mahmoud et al., 2021). Therefore, synaptic transmission in the spinal cord is enhanced, and the response to innocuous stimuli is exaggerated (Neumann et al., 1996). In conformance with literature reports (Bennet and Xie, 1988; Pradhan et al, 2010), data from this study demonstrated that CCI surgery resulted in development of mechanical and cold allodynia in rats from day 3 post CCI surgery. Acute oral treatment of Syringaldehyde at dose of 5, 15, 50 mg/kg on day 7 post surgery has exhibited significant efficacy at 1 h post-treatment. Additionally, 8 day chronic dosing of Syringaldehyde from day 7 to day 14 significantly alleviated allodynia which was assessed on day 10 and day 14. As noted in literature reports, treatment with Gabapentin reversed allodynia in CCI model of neuropathic pain (Rutten et al., 2018).

Biomarker analysis of sciatic nerve showed that increased expression of PGE2, iNOS mRNA levels was seen in ipsilateral sciatic nerve with CCI surgery. Literature reports indicate higher levels of pro-inflammatory pain mediators like COX-2 and PGE2 due to CCI surgery of sciatic nerve in rats (Rezq et al., 2020). Higher expression of COX-2 leads to increased release of PGE2 and higher PGE2 levels increases pain sensitivity and develops neuropathic pain (Ma and Quirion 2005; Mahmoud et al., 2021). Similarly, in this study, CCI surgery led to increased mRNA levels of PGE2 in sciatic nerve at 14 days post-surgery treatment and treatment with Syringaldehyde dose dependently reversed increased levels of these pro-inflammatory pain mediators. Furthermore, CCI induced neuropathic pain is accompanied with increased gene expression levels of iNOS in sciatic nerve (Sobeh et al., 2020). Higher expression of iNOS is known to drive development of neuropathic pain following peripheral nerve injury (Sobeh et al., 2019). At the site of nerve injury, iNOS activation triggers Nitric oxide (NO) release that modulates inflammatory processes and mediates central mechanisms in development of allodynia (Meller et al., 1992). Limiting NO release by inhibition of iNOS is a viable strategy in management of pain (Korhonen et al. 2005.; Gao et al., 2012). Similarly, in this study, chronic treatment with Syringaldehyde reduced elevalted iNOS mRNA levels. Attenuation of neuropathic pain by Syringaldehyde is probably attributed to inhibition of PGE2, iNOS in sciatic nerve.

Summarily, this study demonstrates antiallodynic effects of Syringaldehyde in CCI induced neuropathic pain. Chronic treatment of Syringaldehyde was effective in reversing CCI induced neuropathic pain in rats and inhibited pain biomarkers increased in response to CCI in rats. Thus, going further, Syringaldehyde can be a potential novel therapy for management of neuropathic pain conditions.

Conclusion

This study has demonstrated pharmacological effect of Syringaldehyde in CCI induced neuropathic pain model. Treatment with Syringaldehyde modulates expression of pain mediators to exert its pharmacological effect in CCI induced neuropathic pain model. Data from this study, demonstrates potential of Syringaldehyde as a novel therapeutic option with pharmacological efficacy for treatment of pain.

Conflict of interest
The authors have no conflicts of interest regarding this investigation**.**

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