Original Article

Analgesic and Anti-allodynic Effects of Two Flavonoids in Partial Sciatic Nerve Ligation in Rat Model

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ABSTRACT

Background: Flavonoids, also called as bioflavonoids, are secondary metabolites of plants. Flavonoids, curcumin and hesperidin, possess various pharmacological activities such as analgesic, anti-ulcer, anti-parkinson, anti-cancer, spasmolytic, anti-bacterial, anti-depressant, anti-hypertensive, anti-arthritic and anti-inflammatory. **Aim:** The current study investigated the analgesic and anti-allodynic effects of flavonoids (curcumin and hesperidin) and compared their effects with pregabalin against experimentally induced neuropathic pain in Swiss albino rats. **Methods:** Behavioral parameters were investigated in partial sciatic nerve ligation rat model. Surgery was performed by exposing and ligating the right sciatic nerve. Heat hyperalgesic and cold allodynic tests were assessed using Eddy's hot plate and submerging rat's right hind paw in ice cold water (4 ± 1°C), respectively on days 4,7,10,13,16,19 and 22. Surgery was considered as day 1. Flavonoids and pregabalin (10mg/kg, p.o.) were administered for fifteen days. **Results:** Partial sciatic nerve ligation of right sciatic nerve significantly induced thermal hyperalgesia and cold allodynia. Administration of hesperidin (100mg/kg, p.o.) and curcumin (100mg/kg, p.o.) showed significant increase in paw withdrawal latency in both the behavioral tests. Results of behavioral tests have shown curcumin to be a little more effective than hesperidin in attenuating the neuropathic pain. **Conclusion:** It can be concluded that both hesperidin and curcumin attenuate the neuropathic pain induced by partial sciatic nerve ligation in rats. However, curcumin showed more significant results than hesperidin.

Key words: Flavonoids, Neuropathic pain, Analgesic, Anti-allodynic, Curcumin, Hesperidin, Partial Sciatic Nerve Ligation (PSNL), Hyperalgesic.

INTRODUCTION

Neuropathic pain has been described as 'the most dreadful misery which may levy on a nerve'. It can also be defined as the pain emerged from the nervous system's pathology. It is generally associated with changes in the structure, chemistry and function of neurons.[1,2] Neuropathic pain is caused when an abrasion or disease affects the human body's somatosensory nervous system either peripherally or centrally.[3,4] Central neuropathic pain occurs as a consequence of abnormality affecting specifically the Central Nervous System (CNS) that includes the brain along with brainstem and the spinal cord.[5,6]

Neuropathic pain can occur in people who are suffering or have suffered-Parkinson's disease, spinal cord injuries, brain tumors, strokes, multiple sclerosis, limb amputations or brain injuries. It may evolve several months or years after injury to the CNS. Central neuropathic pain is distinguished by a blend of pain sensations and the most conspicuous characteristic is constant burning. The constant sensation of burning is often elevated by soft touch. Changes in surrounding temperature also heighten the pain, especially cold temperature. The damaged areas can suffer from perception and sensory deficits.[2]

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Peripheral neuropathic pain is generally detected in patients with long-established diseases and disorders like AIDS, diabetes, leprosy, aminotomy, cervical disc protrusion, cancer and after surgery.[7-10] Additionally, post-mastectomy, post-thoracotomy, post-sternotomy and post-herniorrhaphy are other situations which are correlated with peripheral neuropathy.[2,11]

Neuropathic pain is characterized by hyperalgesia (increased pain response to a normally painful stimulus), paraesthesia (abnormal sensation to a stimulus that is normally not unpleasant), dysesthesia (unpleasant abnormal sensation) and allodynia (pain due to a stimulus that normally does not provoke pain).[12-16]

Analgesics (NSAIDs) and different interventional therapies are less powerful in treating neuropathic pain.[17,18] Even though, there are various drugs of different classes available for the productive treatment of neuropathic pain such as antiepileptic drugs, tricyclic antidepressants, sodium channel blockers, botulinum toxin A, opioid agonists and cannabinoid receptor agonists, but their employment is correlated with abundant of side effects.[7] Many drugs have been used to ameliorate this painful condition, but because the underlying mechanisms are multiple, complex and less understood, treatment and management of neuropathic pain requires the employment of different type of medications.[19]

Herbal alternatives have been implicated for the cure of different diseases and disorders since decades. Flavonoid is favorite topic of research of many researchers because of their anti- inflammatory and antioxidant pharmacological activities and they are acknowledged as a positive substitute to down turn neuropathic pain.[20] Curcumin is the major curcuminoid extracted from *Curcuma longa* (turmeric) and has been consumed in food as a curry spice since ancient times.[21] Hesperidin (hesperetin-7- rhamnoglucoside) is found inexpensively and abundantly in citrus species including lemons and sweet oranges.[22-24] Hesperidin and curcumin, both of these flavonoids have been found to own high anti-inflammatory and antioxidant activities and to inhibit the production of inflammatory cytokines, they are utilized for the cure of various inflammatory and neurodegenerative problems of the CNS such as major depression, diabetic neuropathy and alzheimer's disease.[21] Different researchers have investigated an anti-nociceptive effect of both of these flavonoids in neuropathic pain and inflammatory pain.[25]

The effectiveness of curcumin and hesperidin in alleviation of diabetic neuropathic pain has been stated in different studies.[22,26-31] Maximum safe intake values of both flavonoids are very high which assures their least toxic effects.[32-34] Conversion of arachidonic acid to prostaglandins (key mediators in causing pain) is catalyzed by cyclooxygenase-2 (COX-2).[35-37] Allopathic drugs, particularly NSAIDs, are used in severe pain conditions[38] but their usage for long term treatment of neuropathic pain is associated with severe side effects.[39-41] A number of researchers have found that curcumin and hesperidin both acts mainly by impeding the COX-2 pathway.[42-45] Curcumin and hesperidin are also recognized to own antirheumatic and antiarthritic activities, which they exert via down regulation of cyclo-oxygenase-2 and proinflammatory cytokines.[46-48]

Through same way hesperetin, aglycone of hesperidin, alleviated allodynia and hyperalgesia involving reduction of proinflammatory cytokines including TNF-α, IL-1β and IL-6.[49] Both hesperidin and hesperetin have been investigated to have anti-inflammatory activity by a reduction in the levels of iNOS, COX-2, IL-1β and TNF-α via NF-kβ and MAPK pathways.[42] Bioactive ingredients offer some specific therapeutic benefits and less adverse effects. In present context, beneficial effects of flavonoids (namely hesperidin and curcumin) in the treatment of neuropathic pain have been enlightened and their analgesic and anti-allodynic effects have also been compared.

MATERIALS AND METHODS

Experimental Animals

Swiss albino rats (2-3 months, 150-200gm) were procured from the animal house of Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar, Haryana (India). Animals were housed in the animal house of Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra, Haryana (India). The animals were kept in polypropylene cages with wire mesh top and husk bedding. The animals were maintained with 12-h light and 12-h dark cycle and were allowed to acclimatize for two weeks. The animals were housed in a well-ventilated room and standard conditions of temperature (25°**C**±5°C) and humidity (55 ± 10%) were properly maintained. The rats were fed with pellet diet (Ashirwad Industries, Chandigarh). According to CPCSEA (Committee for the Purpose of Control and Supervision on Experimental Animals) guidelines the study protocol (No- IPS/IAEC/2017/304) was approved from Institutional Animal Ethics Committee (IAEC) in the meeting held on 12th Sept' 2017.

Drugs and Chemicals

Ethanol (SD-fine Chemicals Ltd., Mumbai), Carboxy methyl cellulose (Hi Media Laboratories Pvt. Ltd., Mumbai), Curcumin (Hi Media Laboratories Pvt. Ltd.,

Mumbai), Thiopental sodium (Flagship Biotech International Pvt. Ltd., Mumbai), Tween 80 (Hi Media Laboratories Pvt. Ltd., Mumbai), Hesperidin (Sigma Aldrich, USA), Pregabalin (Akums Pvt. Ltd., Haridwar), Antibacterial powder (Cipla Ltd., Delhi) and Povidone iodine (Samrat PharmaChem Ltd., Mumbai) were procured for this study. All the chemicals of analytical grade were used.

Induction of Peripheral Neuropathy by Partial Sciatic Nerve Ligation (PSNL)

The Swiss albino rats were made anesthetized with anesthesia, thiopental sodium (35mg/kg, i.p.). The right hind leg of the rat was shaved along with lower back in its thigh region. The shaved area was sterilized with 70% isopropyl alcohol. An incision was performed in the skin 3-4 mm below the femur of right thigh and the skin was separated from the muscle around the incision. A cut was applied directly through the muscles and the sciatic nerve of the rat was exposed. Single ligation of approx. 1/3 to 1/2 of the diameter of sciatic nerve was performed with chromic gut 4.0. Catgut 4.0 or chromic gut 4.0 sutures were utilized to suture the open muscle layer and mersilk 5.0 to affix the skin. Next, povidone-iodine solution was used to sterilise the wound and antibiotic powder (Clocip) was applied on the wound as well.[49]

Experimental Protocol

Five groups were employed in the current study, each containing six Swiss albino rats. Rats were distributed among the following below mentioned groups:

Group-1 (Normal Control): No ligation.

Group-2 (Control): No drug (PSNL)

Group-3 (Standard): Pregabalin (PSNL)

Group-4 (Test group-1): Curcumin (PSNL)

Group-5 (Test group-2): Hesperidin (PSNL)

All the drugs were prepared freshly every time before administration. Particular dose of each flavonoid was given to different test groups. Pregabalin (standard drug) was given to standard group. Test and standard drugs were administered for 15 days after ligation. Surgery was considered as day 1. Behavioral tests were assessed on days 4,7,10,13,16,19 and 22.

Behavioral Parameters

Heat Hyperalgesic Test

Heat hyperalgesic test was executed for right hind paw and was evaluated with the help of Eddy's hot plate. The animals were kept on Eddy's hot plate which was preheated and retained at 52.5 ± 0.5°C. Paw withdrawal latency (paw licking or brisk running) was observed and noted. Cutoff time of 20s was fixed.[50]

Cold Allodynia Test

In this behavioral examination the rat's right hind paw was submerged in a beaker containing ice cold water maintained at 4 ± 1°C. The rat's paw withdrawal latency was examined. The maximum cutoff time was of 20s.[49]

Dose Selection

Dose was selected according to acute toxicity LD_{50} study which states that the LD_{50} is higher than 2000 mg/kg for both flavonoids' hesperidin[33] and curcumin.[34] One tenth of 2000 mg/kg dose was selected for preliminary animal studies.

RESULTS

Effect on Heat Hyperalgesia

In heat hyperalgesic test, control group animals which were subjected to PSNL exhibited statistically significant decline in time of paw withdrawal latency to heat stimulus as observed on first behavioral test day (i.e. 4th day of the study) and continued throughout the study. This nature indicates the introduction of thermal hyperalgesia. Antagonistically, detection of zero statistically significant change in withdrawal latency was there in normal control group (P<0.001), whereas treatment with pregabalin (10mg/kg, p.o.), hesperidin and Curcumin (100mg/kg, p.o.) increases paw withdrawal latency (P<0.001) till the termination of the study as compared to control. Results are shown in Figure 1.

Effect on Cold Allodynia

In cold allodynia test, the control group that was subjected to PSNL exhibited statistically significant

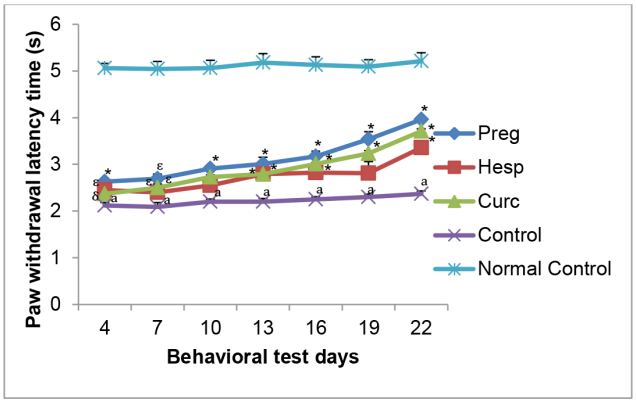

Figure 1: Effect of hesperidin (100mg/kg, p.o.), curcumin (100mg/kg, p.o.) and pregabalin (10mg/kg, p.o.) on paw withdrawal latency in heat hyperalgesic test.

Data expressed as mean ± SEM., n = 6 i.e. 6 rats in each group. Data was analyzed using two-way ANOVA. *: P< 0.001, ε: P< 0.01, δ: P< 0.05 as compared to control, a: P< 0.001 as compared to normal control.

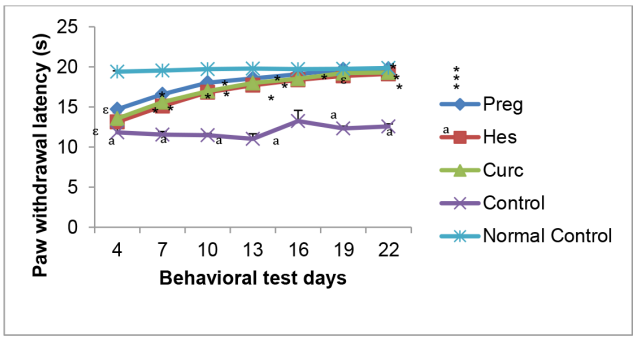

Figure 2: Effect of hesperidin (100mg/kg, p.o.), curcumin (100mg/kg, p.o.) and pregabalin (10mg/kg, p.o.) on paw withdrawal latency in cold allodynia test.

Data expressed as mean ± SEM., $n = 6$ i.e. 6 rats in each group. Data was analyzed using two-way ANOVA. *: $P< 0.001$, ε: $P< 0.01$ as compared to control, a: $P< 0.001$ as compared to normal control.

decline in paw withdrawal latency from first day of behavioral test to last day test which proved the introduction of cold allodynia. While in normal control group No significant change was noted. Significant upturn in paw withdrawal latency time was noticed ($p<0.001$) by administration of hesperidin and curcumin during the study. In similar manner, pregabalin also significantly elevated paw withdrawal latency ($p<0.001$) as compared to control, throughout the study. Results are shown in Figure 2.

DISCUSSION

In different epidemiological studies of India from several territories and regions the overall pervasiveness of peripheral neuropathy fluctuates from 5 to 2400 per ten thousand people.[51] Neuropathic pain has high prevalence in other countries too. Studies conducted in France and Alberta stated that around 7-18% of the population suffers from incessant neuropathic pain which arises from damage to central or peripheral nervous system.[52-54] PSNL is universally excepted model to induce neuropathic pain as it imitates the chronic nerve compression's pathology in human beings. GABA has Pregabalin as its structural analog but not functional.[55] Many studies have stated that pregabalin has anxiolytic, anti-oxidant, analgesic and anti-inflammatory activities in rodents[56-58] along with anti-allodynic and anti-hyperalgesic activities in several neuropathic pain models.[59,60] Inclusions of several mechanisms in the pathogenesis of neuropathic pain have been shown by various researchers. These mechanisms possibly interact in the patient's body making the disease more complex.[61] Oxidative stress and formation of ROS (reactive oxygen species) both are acknowledged as the main pathways through which neuropathic pain arises.[62]

From past several studies it has been found that flavonoids, curcumin and hesperidin, show promise as useful adjuvant to prevent, delay and/or ameliorate several diseases in humans. These biological compounds are famous for various pharmacological activities which have to be recognized particularly in this study for mitigating the neuropathic pain and recognizing mediators in their pharmacological response. In present work, we have figured out the potential efficacy of systemic administration of curcumin and hesperidin in PSNL induced neuropathic pain in Swiss albino rats. Single ligation of sciatic nerve induced marked behavioral changes in cold and thermal allodynia. Treatment either with standard pregabalin (10mg/kg, p.o.) or test drugs hesperidin (100 mg/kg, p.o.) and curcumin (100 mg/kg, p.o.) attenuated cold and thermal hyperalgesia. Firstly, in this study a significant nociceptive response in both cold and thermal hyperalgesia was observed in the experimental neuropathic rats from control group after PSNL induction in comparison with normal control rats. Whereas, rats that were given hesperidin (100 mg/kg, p.o.) and curcumin (100 mg/kg, p.o.) demonstrated a significant reduced hyperalgesia. This work shows that the PSNL group exhibited marked reduction in paw withdrawal latency and of paw withdrawal threshold as compared with normal control group. Whereas, till the end of the study treatment with pregabalin (10mg/kg, p.o.), hesperidin and curcumin (100mg/kg, p.o.) increased paw withdrawal latency and paw withdrawal threshold as compared to control. However, curcumin showed more impressive and positive results than hesperidin.

CONCLUSION

It can be concluded that both hesperidin and curcumin attenuate the neuropathic pain induced by partial sciatic nerve ligation in rats. Moreover, behavioral test results have shown curcumin to be a little more effective than hesperidin in attenuating the neuropathic pain caused by PSNL.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

PSNL: Partial Sciatic Nerve Ligation; **CNS:** Central Nervous System; **NSAIDs:** Non-Steroidal Anti-Inflammatory Drugs; **COX-2:** Cyclooxygenase-2; **TNF-α:** Tumour Necrosis Factor-α; **IL-1β:** Interleukin-1β; **IL-6:** Interleukin-6; **iNOS:** Inducible nitric oxide synthase; **NF-kβ:** Nuclear Factor kappa-light-chain-enhancer of activated β cells; **MAPK pathway:** Mitogen-Activated Protein Kinase pathway; **ED_{50}:** Median Effective Dose; **LD_{50}:** Median Lethal Dose; **ROS:** Reactive Oxygen Species; **GABA:** Gamma Amino Butyric Acid.

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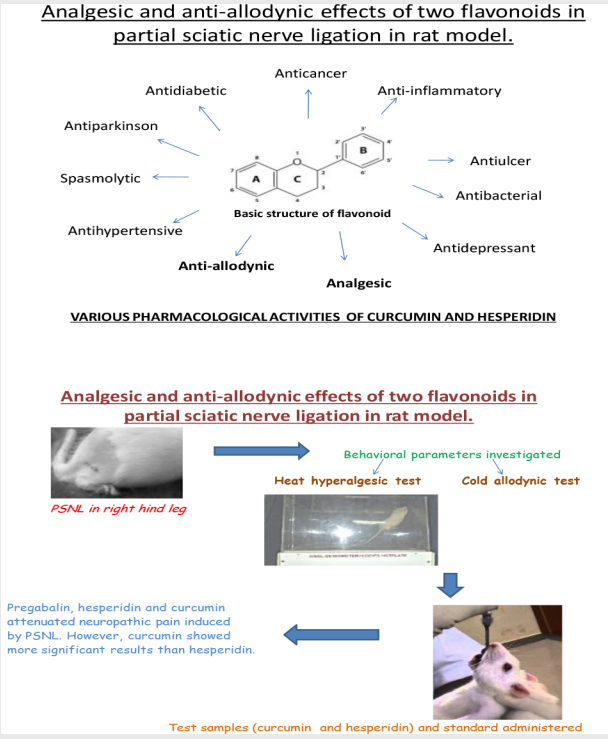
PICTORIAL ABSTRACT



SUMMARY

Neuropathic pain is one of the most severe types of chronic pain and has high pervasiveness around the globe. Thus it is absolutely important to derive effective and potent medicines and various ways of treatment to curtail fatality rate and enhance the diagnosis and living standard of the sufferer. In present work, we showed that both hesperidin and curcumin attenuate the neuropathic pain induced by partial sciatic nerve ligation in rats. Additionally, curcumin has shown more significant behavioral test results than hesperidin in attenuating and crippling the neuropathic pain caused by PSNL.

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