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Effect of Epigallocatechin Gallate (EGCG) as an Adjuvant to Paracetamol on Pain Scale and TRPV1 Expression in a Rat Model of Neuropathic Pain

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ABSTRACT

Background & Objective: Neuropathic pain remains challenging to treat due to peripheral and central sensitisation involving oxidative stress, neuroinflammation, and dysregulation of ion channels such as transient receptor potential vanilloid 1 (TRPV1). Epigallocatechin gallate (EGCG), the major catechin in green tea, has antioxidant and anti-inflammatory properties that may complement the central analgesic effects of paracetamol. This study examined whether EGCG enhances paracetamol's analgesic efficacy in a chronic constriction injury (CCI) model of neuropathic pain, by assessing mechanical pain thresholds and TRPV1 expression.

Methods: This experimental study used male Wistar rats (150–200 g, 2–2.5 months old) with neuropathic pain induced by Chronic Constriction Injury (CCI) of the right sciatic nerve. The rats were assigned to three groups: control, paracetamol (200 mg/kgBW), and paracetamol + EGCG (40 mg/kgBW). Pain threshold was assessed using the Electronic Von Frey Test, and TRPV1 levels were measured by ELISA. Data were analyzed with ANOVA and Spearman correlation tests.

Results: The combination of paracetamol and EGCG significantly lowered TRPV1 levels and increased pain threshold compared to other groups ($p < 0.05$). TRPV1 expression was highest in the control and lowest in the combination group. A strong negative correlation was found between TRPV1 levels and pain intensity ($rs = –0.711$; $p = 0.010$), indicating that reduced TRPV1 was associated with less pain.

Conclusions: EGCG enhances the antinociceptive effects of paracetamol by reducing TRPV1 expression and improving nociceptive behaviour. EGCG shows potential as a safe, non-opioid adjuvant for neuropathic pain management.

KEYWORDS: EGCG, paracetamol, neuropathic pain, TRPV1, chronic constriction injury.

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INTRODUCTION

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, serving an essential protective role in preventing further harm. In clinical practice, pain is categorised as nociceptive, neuropathic, psychogenic, or nociplastic, providing diagnostic clarity and guiding treatment decisions.[1] Chronic neuropathic pain is a complex and debilitating condition resulting from structural or functional lesions within the somatosensory nervous system, frequently manifesting as burning, shooting, or electric-shock sensations.[2] Its global prevalence is estimated at 10–20%, with rising incidence linked to ageing populations and chronic diseases such as diabetes.[3] It imposes a substantial burden on patients' quality of life and remains notoriously challenging to manage effectively.

Conventional pharmacological strategies often rely on a spectrum of agents, including anticonvulsants, antidepressants, and opioids. However, the utility of these drugs is severely limited by common adverse effects such as sedation, dizziness, and the risk of dependency and tolerance with prolonged use.[4] This highlights a critical need for safer, well-tolerated agents that can serve as an adjuvant to paracetamol and other standard analgesics, thereby enhancing efficacy while permitting dose-sparing strategies. The underlying pathology of neuropathic pain involves dynamic peripheral and central sensitization processes sustained by neuroinflammation, oxidative stress, and the dysregulation of key ion channels.[5] A central molecular target in this process is the Transient Receptor Potential Vanilloid 1 (TRPV1) channel. Following nerve injury, the upregulation and sensitization of TRPV1 drives calcium influx and enhanced neurotransmitter release, directly contributing to the hyperalgesia and allodynia that are quantitatively measured using specialized pain scales (e.g., electronic von Frey).[6] Pharmacologically targeting TRPV1 to achieve its down-regulation is a rational strategy to reduce neuronal hyperexcitability and reverse key features of neuropathic pain.[5]

Indonesia's rich biodiversity offers immense potential for phytopharmacological innovation. Epigallocatechin gallate (EGCG), the principal polyphenol in green tea (*Camellia sinensis*), possesses potent antioxidant and neuroprotective actions.[7] EGCG's mechanisms include suppressing the generation of reactive oxygen species (ROS)[8] and inhibiting inflammatory signaling pathways such as MAPK-mediated and NF-κB pathways.[9] Experimental studies further show that EGCG reduces TRPV1 expression and improves neuropathic pain behaviours in rodent models.[10] Given that EGCG has demonstrated the capacity to modulate neuroinflammation, its pleiotropic effects are hypothesized to converge on the pathways responsible for TRPV1-driven

peripheral sensitization.[11]

Paracetamol remains widely used as a first-line analgesic due to its favourable safety profile. Its primary action involves central prostaglandin synthesis inhibition and neuromodulation within descending serotonergic pathways.[12] Combining paracetamol with a peripheral modulator such as EGCG offers a mechanistically complementary approach: paracetamol targeting central nociception, and EGCG mitigating TRPV1-mediated peripheral sensitisation.

Despite the compelling, complementary mechanisms, EGCG's peripheral anti-inflammatory profile combined with paracetamol's central neuromodulatory action of direct evidence evaluating EGCG as an adjuvant to paracetamol in preclinical models of neuropathic pain is critically limited. Crucially, studies linking EGCG treatment directly to the modulation of TRPV1 expression and corresponding improvements in behavioral pain scales are sparse. Therefore, this study aims to analyze the analgesic effect of epigallocatechin gallate (EGCG) as an adjuvant to paracetamol on pain behavior and TRPV1 expression in a chronic constriction injury rat model of neuropathic pain.

METHODOLOGY

This study was an experimental, post-test-only randomized controlled laboratory study conducted to evaluate the analgesic effect of epigallocatechin gallate (EGCG) as an adjuvant to paracetamol in a rat model of neuropathic pain. The experiment was carried out at the Institute of Tropical Disease, Universitas Airlangga approved by the Ethics Committee of the Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia (Ethics No. 2.KEH.98.06.2025).

Animals

The sample size was calculated using the hypothesis testing formula for population means with a two-tailed design, as this study aimed to detect differences in the analgesic effect of EGCG as an adjuvant to paracetamol on pain scores and TRPV1 expression without assuming the direction of the effect. A significance level of $\alpha = 0.05$ ($Z\alpha = 1.96$) and a statistical power of 80% ($Z\beta = 0.84$) were applied. The standard deviation (σ) of 1.30 g and the minimum clinically meaningful difference (δ) of 2.75 g were determined based on previous studies using the neuropathic pain model. Using the formula $n = 2 (Z\alpha + Z\beta)^2 \times \sigma^2 / \delta^2$, a minimum of 4 rats per group was obtained. With three treatment groups, a total of 12 male Wistar rats were included in this study.

Animals were acclimatized for seven days under controlled environmental conditions (22 ± 2 °C, 12-hour light–dark cycle) with ad libitum access to food and water. All treatments were administered orally once daily for seven consecutive days. Following acclimatization, animals were randomly allocated into three groups (n = 4 per group). To minimize potential confounders, animals were housed in identical cages and rotated daily to prevent location bias resulting from variations in light or temperature. All behavioral assessments and tissue sampling were performed in random order.

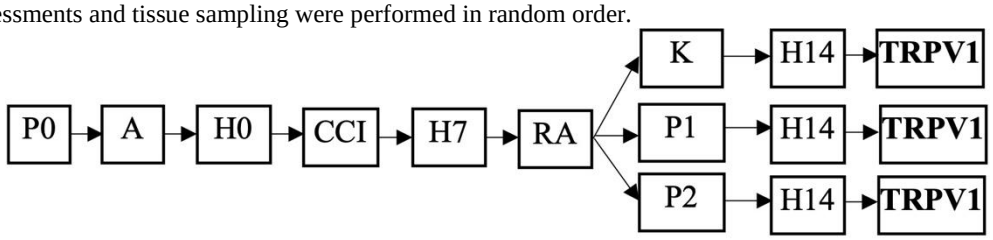

Figure 1. Research study scheme

P0: population; A: acclimatization; H0: Von Frey test baseline; CCI: chronic constriction injury for animal pain model; H7: Von Frey test a week after induction; RA: randomization; K: received placebo (CMC-Na 1%); P1: received paracetamol 200 mg/kg/day; P2 : received paracetamol 200 mg/kg/day + ECGC 40 mg/kg/day; h14: Von Frey test day 14; TRPV1: mice terminated then TRPV1 measured.

Chronic Constriction Injury Procedure

Neuropathic pain was induced using the chronic constriction injury (CCI) model, as previously described by earlier research.[13] Under anaesthesia with a ketamine/xylazine/acepromazine mixture (60 mg/kg, 7.5 mg/kg, 1 mg/kg i.p., respectively), the right sciatic nerve was exposed at the mid-thigh level and loosely ligated with four 5-0 safyl monofilament sutures, spaced approximately 1 mm apart. The incision was then closed with sterile sutures and disinfected with povidone-iodine.

Preparation of Drug Suspensions

EGCG (≥98.7% purity; Xi'an Rongsheng Biotechnology, China) was dissolved in distilled water to prepare stock suspensions of 8 mg/mL, then diluted to 4 mg/mL and 1 mg/mL as required for dosage adjustment. Paracetamol was prepared by suspending the powdered compound in 1% CMC-Na to yield a concentration of 40 mg/mL. All suspensions were freshly prepared and stored in sterile vials at 4 °C prior to administration.

Behavioral Assessment of Mechanical Allodynia

Pain response was evaluated using the Von Frey filament test.[14] Rats were placed in elevated wire mesh chambers and allowed to acclimate for 60 minutes. Calibrated filaments were applied perpendicularly to the plantar surface of the hind paw until the filament bent slightly. The withdrawal threshold (in gram-force) was recorded for both hind paws at three time points: baseline (day 0), post-injury (day 7), and post-treatment (day 14). Each test was performed three times, and the mean value was used for

analysis.

TRPV1 Quantification

At day 14, animals were euthanized, and brain tissue was collected for TRPV1 protein quantification. Quantitative measurement of TRPV1 protein in rat brain tissue was conducted using a sandwich ELISA method employing monoclonal and polyclonal antibodies specifically designed to recognize TRPV1 from both human and rat sources. The monoclonal antibody 10E3-1A2 targets the TRPV1 epitope at amino acids 45–58, while polyclonal TRPV1 antibody ABRK4 serves as the capture antibody, enabling a dual-species detection platform. Recombinant human TRPV1 protein, produced heterologous in mammalian HEK293-F cells and purified via affinity chromatography, was used as the calibration standard, with assay sensitivity reaching 1.5 ng/mL (15 pM). Brain tissues were collected, cut into small pieces, and rinsed with cold PBS (0.01 M, pH 7.4) to remove excess blood before homogenization in PBS at a 1:9 tissue-to-volume ratio on ice. The homogenates were centrifuged at 5000 × g for 5–10 minutes at 2–8 °C to obtain the supernatant. TRPV1 concentrations in the homogenates were determined using an ELISA kit (MBGAM0001, MEDIKBIO PT GAMA BIOTEK, Malang, Indonesia) following the manufacturer's protocol, and absorbance was measured at 450 nm using a microplate reader, with results expressed in ng/mL.

Data Processing and Statistical Analysis

All data were analyzed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Data normality was assessed using the Shapiro–Wilk test. Normally distributed data were analyzed with one-way ANOVA, whereas nonparametric data were analyzed using the Kruskal–Wallis test followed by Mann–Whitney post hoc comparisons. Statistical significance was set at $p < 0.05$. Graphs were generated using GraphPad Prism 9.0. The full dataset and analysis scripts are available upon reasonable request to the corresponding author.

RESULTS

TRP levels

The TRPV1 levels in brain homogenates were measured using ELISA for three groups: Control (K), Paracetamol (P1), and Paracetamol + EGCG 40 mg/kg (P2). A total of 15 animals were initially included, but due to exclusion criteria and technical issues, the final analysis was based on 4 valid samples per group. Shapiro-Wilk tests were performed to assess the normality of the TRPV1 data. Based on the normality test, TRPV1 data in the control group were not normally distributed; therefore, comparisons among the three groups were analyzed using the Kruskal–Wallis test.

Table 1. Statistical Comparison of TRPV1 Levels Between Groups

Variable	N	Median (range)	p-value
K	4	1.58 (1.56 – 2.02)	
P1	4	2.61 (2.00 – 3.07)	0.010
P2	4	1.43 (1.40 – 1.45)	

The Kruskal-Wallis test revealed a significant difference in TRPV1 levels between the three groups (p = 0.010). Mann-Whitney post-hoc analysis indicated significant differences between Control and P1 (p = 0.043), Control and P2 (p = 0.020), and P1-P2 (p=0,020) with the Paracetamol group (P1) showing the highest TRPV1 levels.

The Paracetamol group (P1) showed the highest TRPV1 levels, suggesting that Paracetamol alone may stimulate TRPV1 expression. In contrast, the Paracetamol + EGCG group (P2) exhibited the lowest TRPV1 levels, indicating a potential synergistic

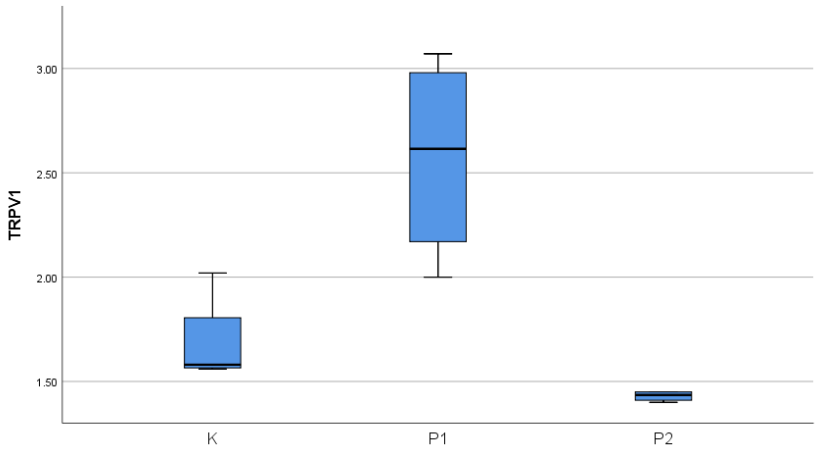

Figure 1. Box plot of TRPV1 levels among intervention groups

effect where EGCG may reduce TRPV1 expression, contributing to pain relief. The Control group (K) had intermediate TRPV1 levels, confirming that the treatment interventions significantly altered TRPV1 expression compared to the baseline. These findings suggest that EGCG modulates the TRPV1 pathway in combination with Paracetamol, potentially enhancing its analgesic effects.

Von Frey test

The Von Frey test was used to measure the pain threshold at three time points: baseline (before intervention), post-CCI (after chronic constriction injury), and post-treatment (after administration of the respective treatments). To ensure group homogeneity before the intervention, a pairwise comparison of baseline pain scores was conducted using the Mann-Whitney test. The results revealed no statistically significant differences in baseline pain scores between any group pairs. Specifically, the comparison between the Control (K) and Paracetamol (P1) groups yielded a p-value of 0.083, between the Control (K) and Paracetamol + EGCG (P2) groups a p-value of 0.149, and between the Paracetamol (P1) and Paracetamol + EGCG (P2) groups a p-value of 0.248. These findings confirm that the baseline pain levels were comparable across all groups prior to the intervention.

Table 2. Von Frey test

Group	Control (K)	Paracetamol (P1)	Paracetamol + EGCG (P2)	*p* Value
Baseline	3.15 (1.67 - 4.96)	5.02 (4.12 - 5.89)	7.21 (1.67 - 7.39)	0.138[a]
Post CCI	0.66 ± 0.28	0.48 ± 0.16	1.20 ± 0.88	0.201[b]
Post Treatment	1.48 ± 0.59	1.61 ± 0.93	4.97 ± 2.67	0.026[b]

a : Kruskall Wallis test, b : Analysis of Variance, Median (Range), Mean ± SD

At baseline, the Control (K) group exhibited a mean Von Frey value of 3.23 ± 1.35 with a median of 3.15 (1.67 – 4.96). The Paracetamol (P1) group showed a higher mean value of 5.01 ± 0.95, with a median of 5.02 (4.12 – 5.89). The Paracetamol + EGCG (P2) group had the highest mean of 6.14 ± 2.27, with a median of 7.21 (1.67 – 7.39). Following CCI, all groups showed a reduction in pain threshold. After treatment, the Paracetamol + EGCG (P2) group had a significantly higher mean of 4.97 ± 2.67, with a median of 4.13 (2.84 – 8.80).

There were no significant differences were observed in Von Frey values between the three groups (p = 0.138 for K vs P1, p = 0.249 for K vs P2, and p = 0.248 for P1 vs P2) at baseline. However, following post-CCI, the pain thresholds decreased across all groups, with the Paracetamol + EGCG (P2) group showing a trend towards higher pain sensitivity compared to the other groups. At post-treatment, there was a significant difference in Von Frey values between the groups (p = 0.026). Pairwise comparisons revealed that the Paracetamol + EGCG (P2) group exhibited a significantly higher pain threshold than both the Control (K) and Paracetamol (P1) groups, with p = 0.016 and p = 0.019, respectively. However, no significant difference was observed between the Control (K) and Paracetamol (P1) groups (p = 0.919). Overall, the Paracetamol + EGCG (P2) group demonstrated the most significant improvement in pain threshold, suggesting a potential synergistic effect between Paracetamol and EGCG in modulating pain sensitivity in this neuropathic pain model.

Spearman's rank correlation analysis revealed a significant negative relationship between brain TRPV1 levels and mechanical pain threshold measured by the Von Frey test (*rs* = –0.711, *p* = 0.010). This finding indicates that higher TRPV1 expression was associated with a lower Von Frey threshold, reflecting greater pain sensitivity. Conversely, lower TRPV1 levels corresponded to an increased pain threshold, suggesting attenuation of neuropathic pain. The magnitude of the correlation coefficient demonstrates a strong inverse association between TRPV1 activity and pain response. This negative correlation is illustrated in Figure 5.5, where the regression line displays a downward slope, confirming that variations in brain TRPV1 expression are closely related to alterations in mechanical pain threshold in neuropathic pain model rats treated with EGCG as an adjuvant to paracetamol.

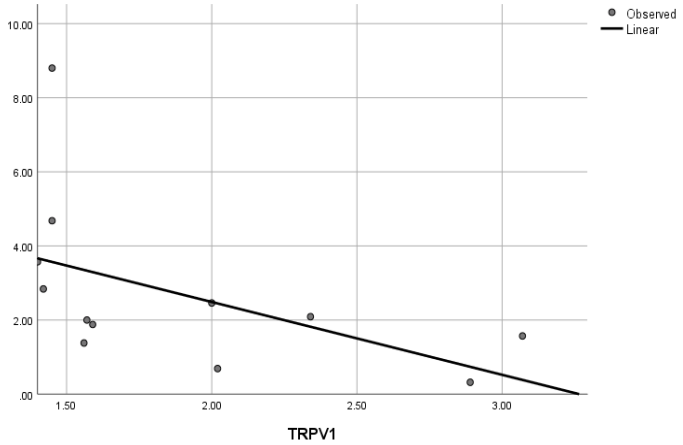

Figure 2. *Von Frey* and TRPV1 scatter plot

DISCUSSIONS

This study demonstrated that epigallocatechin gallate (ECGC) enhances the analgesic efficacy of paracetamol in a rat model of neuropathic pain induced by chronic constriction injury (CCI). Animal model are the key for understanding the neuropathic pain mechanism, therefore developing effective and comprehensive therapy.[15] This behavioural improvement was accompanied by a dose-dependent reduction in TRPV1 expression in brain tissue homogenates, indicating that TRPV1 modulation contributes to the analgesic synergy. These findings are consistent with the well-established role of TRPV1 in neuropathic pain hypersensitivity

and central sensitization, where increased TRPV1 signalling amplifies nociceptive transmission and pain perception.

Neuropathic pain is commonly associated with peripheral and central sensitization mediated by TRPV1 upregulation. TRPV1 contributes to enhanced glutamate release, increased intracellular calcium, and hyperexcitability of nociceptive neurons, leading to reduced trigger thresholds and abnormal pain perception.[5] Consistent with these mechanisms, CCI significantly increased TRPV1 expression in the control group. Treatment with EGCG alone attenuated TRPV1 expression in a dose-dependent manner, which aligns with previous findings showing EGCG's ability to modulate TRPV1 activity, reduce oxidative stress, and inhibit pro-inflammatory mediators such as TNF-α and IL-1β. These mechanisms collectively contribute to reduced neuronal sensitization and pain transmission.[16,17]

EGCG is a potent antioxidant that neutralises excessive ROS/RNS and enhances endogenous antioxidant defences such as superoxide dismutase (SOD), thereby protecting neurons from oxidative injury that contributes to neuropathic sensitisation. It also suppresses NF-κB–driven neuroinflammation, reducing cytokines such as TNF-α and IL-6 that promote pain signalling. EGCG further supports axonal repair and inhibits apoptosis during peripheral nerve injury, while improving tissue remodelling through enhanced fibroblast proliferation, collagen synthesis, and angiogenesis. These complementary antioxidant, anti-inflammatory, and neuroprotective actions mechanistically underpin the dose-responsive benefits observed in the current study.[18]

Paracetamol exerts its analgesic effects largely through central mechanisms, involving the inhibition of prostaglandin synthesis, enhancement of serotonergic activity, and modulation of the endocannabinoid system. However, its efficacy in neuropathic pain is limited when used as monotherapy.[17] In this study, paracetamol alone produced only moderate improvement in mechanical thresholds, supporting its limited role in neuropathic pain management. When combined with EGCG, analgesic outcomes were significantly greater than either agent alone, indicating a synergistic interaction. Paracetamol activates TRPV1 in the spinal cord through metabolic AM404, which increases pain sensitivity if not compensated by other mechanisms.[12] EGCG has strong anti-inflammatory and antioxidant activities, suppresses TRPV1 activation, particularly in the periphery, and reduces the release of pro-inflammatory cytokines and pain mediators.[19] Thus, EGCG acts as a functional antagonist against paracetamol-induced TRPV1 activation, thereby enhancing the overall analgesic effect.

The negative correlation between TRPV1 expression and mechanical threshold further supports TRPV1 as a functional biomarker of analgesic effect in neuropathic states. TRPV1 is a key mechanistic link between treatment intervention and nociceptive outcomes, as evidenced by the moderate but statistically significant correlation ($r_s = –0.711$; $p = 0.010$) that lower TRPV1 levels are associated with improved pain behavior. Our results add to the body of evidence showing that green tea polyphenols have analgesic and neuroprotective properties.[8] They also suggest that EGCG enhances the effectiveness of paracetamol by blocking maladaptive nociceptive pathways. Additionally, EGCG has been shown to improve endogenous antioxidant defenses and lessen mitochondrial dysfunction, which may help prevent long-term neuronal damage following nerve injury.[18] Given that neuropathic pain frequently involves enduring inflammatory and oxidative processes that conventional analgesics are unable to effectively address, this multimodal mechanism is especially pertinent.

This synergy is not only demonstrated through TRPV1 receptor modulation but also in terms of target organ protection. High doses of paracetamol carry a risk of hepatotoxicity due to the formation of the reactive metabolite NAPQI, whereas EGCG can neutralize ROS, reduce the formation of NAPQI-protein adducts, and restore mitochondrial electron transport chain function.[20] Thus, the combination of the two provides a double benefit, namely increasing analgesic efficacy through a synergistic mechanism in the pain pathway while reducing the risk of systemic side effects. These findings support the use of a combination of paracetamol and EGCG as a multimodal therapeutic strategy that is safer and more effective than the use of paracetamol alone.

From a translational standpoint, neuropathic pain treatment benefits from the combination of EGCG and paracetamol. A naturally occurring substance with a good safety record, EGCG may help save paracetamol doses, lowering the risk of hepatotoxicity that comes with excessive or long-term use. Furthermore, TRPV1 and central pain pathways are targeted in accordance with contemporary multimodal analgesia techniques, which limit side effects while offering additive or synergistic benefits.

LIMITATIONS

This study has limitations, despite its encouraging findings. Because TRPV1 measurement was limited to brain homogenates, changes within particular nociceptive nuclei could not be localized. Mechanistic depth is limited by the lack of electrophysiological or immunohistochemical validation. Longer treatment periods and evaluation of functional recovery outside of nociceptive response may also improve the interpretation of neuroprotective effects.

CONCLUSION

ECGC administered as adjuvant to paracetamol improved mechanical allodynia and reduced TRPV1 in a rat CCI model. These data support further translational investigation of EGCG as an adjuvant analgesic for neuropathic pain.

Data availability: The data and materials generated during this research is available by the corresponding authors

Ethical considerations: The research followed a protocol authorized by a local ethics committee at Animal Care and Use Committee, Faculty of Veterinary Medicine, Universitas Airlangga (No: 2.KEH.98.06.2025).

Conflict of interest: All authors declare that there was no conflict of interest

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REFERENCES

1. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain.* 2020;161(9):1976–82.
2. Petroianu GA, Aloum L, Adem A. Neuropathic pain: mechanisms and therapeutic strategies. *Front Cell Dev Biol.* 2023;11.
3. Smith BH, Hébert HL, Veluchamy A. Neuropathic pain in the community: prevalence, impact, and risk factors. *Pain.* 2020;161(Suppl 1):S127–37.
4. Rosenberger DC, Blechschmidt V, Timmerman H, Wolff A, Treede R-D. Challenges of neuropathic pain: focus on diabetic neuropathy. *J Neural Transm.* 2020;127(4):589–624.
5. Ma Y-C, Kang Z-B, Shi Y-Q, Ji W-Y, Zhou W-M, Nan W. The complexity of neuropathic pain and central sensitization: exploring mechanisms and therapeutic prospects. *J Integr Neurosci.* 2024;23(5).
6. Mumpuni DR, Putri HS, Airlangga PS, Waloejo CS, Santoso KH, Lestari P. Transient receptor potential vanilloid 1 in acute pain: a literature review. *Pharmacogn J.* 2024;16(5):1196–201.
7. Xifró X, Vidal-Sancho L, Boadas-Vaello P, Turrado C, Alberch J, Puig T, et al. Novel epigallocatechin-3-gallate (EGCG) derivative as a new therapeutic strategy for reducing neuropathic pain after chronic constriction nerve injury in mice. *PLoS One.* 2015;10(4):e0123122.
8. Michalak B, Piwowarski JP, Granica S, Waltenberger B, Atanasov AG, Khan SY, et al. Eupatoriopicrin inhibits pro-inflammatory functions of neutrophils via suppression of IL-8 and TNF-α production and p38 and ERK1/2 MAP kinases. *J Nat Prod.* 2019;82(2):375–85.
9. Wang J, Yu Z, Hu Y, Li F, Huang X, Zhao X, et al. EGCG promotes sensory function recovery in rats after dorsal root crush injury by upregulating KAT6A and inhibiting pyroptosis. *Transl Neurosci.* 2023;14(1).
10. Bimonte S, Cascella M, Schiavone V, Mehrabi-Kermani F, Cuomo A. The roles of epigallocatechin-3-gallate in the treatment of neuropathic pain: an update on preclinical in vivo studies and future perspectives. *Drug Des Devel Ther.* 2017;11:2737–42.
11. Chen X, Le Y, Tang S-Q, He W-Y, He J, Wang Y-H, et al. Painful diabetic neuropathy is associated with compromised microglial IGF-1 signaling which can be rescued by green tea polyphenol EGCG in mice. *Oxid Med Cell Longev.* 2022;2022:1.
12. Mallet C, Desmeules J, Pegahi R, Eschalier A. An updated review on the metabolite (AM404)-mediated central mechanism of action of paracetamol (acetaminophen): experimental evidence and potential clinical impact. *J Pain Res.* 2023;16:1081–94.
13. Dias QM, Rossaneis AC, Fais RS, Prado WA. An improved experimental model for peripheral neuropathy in rats. *Braz J Med Biol Res.* 2013;46(3):253–6.
14. Deuis JR, Dvorakova LS, Vetter I. Methods used to evaluate pain behaviors in rodents. *Front Mol Neurosci.* 2017;10.
15. Jaggi AS, Jain V, Singh N. Animal models of neuropathic pain. *Fundam Clin Pharmacol.* 2011;25(1):1–28.
16. Siracusa R, Monaco F, D'Amico R, Genovese T, Cordaro M, Interdonato L, et al. Epigallocatechin-3-gallate modulates postoperative pain by regulating biochemical and molecular pathways. *Int J Mol Sci.* 2021;22(13):6879.
17. Ayoub SS. Paracetamol (acetaminophen): a familiar drug with an unexplained mechanism of action. *Temperature.* 2021;8(4):351–71.
18. Mokra D, Joskova M, Mokry J. Therapeutic effects of green tea polyphenol (–)-epigallocatechin-3-gallate (EGCG) in relation to molecular pathways controlling inflammation, oxidative stress, and apoptosis. *Int J Mol Sci.* 2022;24(1):340.
19. Machova Urdzikova L, Ruzicka J, Karova K, Kloudova A, Svobodova B, Amin A, et al. A green tea polyphenol epigallocatechin-3-gallate enhances neuroregeneration after spinal cord injury by altering levels of inflammatory cytokines. *Neuropharmacology.* 2017;126:213–23.
20. Zhang M, Ma Y, Ye X, Zhang N, Pan L, Wang B. TRP ion channel family: structures, biological functions and therapeutic interventions for diseases. *Signal Transduct Target Ther.* 2023;8(1):261.