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Synergistic Effect of Cacao Extract and Pregabalin on TNF-α and ERK MAPK Expression in a Rat Model of Neuropathic Pain

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Abstract: *Neuropathic pain remains a major clinical challenge due to its persistence and poor response to conventional analgesics. This experimental study aimed to evaluate the synergistic potential of cacao extract combined with pregabalin in modulating peripheral and central sensitization markers in a rat model of neuropathic pain induced by chronic constriction injury (CCI). Four groups were studied: control group (K-) received placebo, treatment group 1 (K1) received pregabalin 60mg/kgBW, treatment group 2 (K2) received pregabalin 60mg/kgBW + cacao extract 1mg/gBW, and treatment group 3 (K3) received pregabalin 30mg/kgBW + cacao extract 1mg/gBW. Serum levels of tumor necrosis factor-alpha (TNF-α) and brain expression of extracellular signal-regulated kinase (ERK) were assessed alongside mechanical allodynia using von Frey filament testing. The CCI + Placebo group showed marked elevations in TNF-α and ERK levels, accompanied by severe mechanical allodynia. Pregabalin monotherapy moderately reduced these markers and improved pain thresholds. The combination therapies produced the most substantial reductions in TNF-α and ERK expression and significantly improved von Frey thresholds, indicating attenuation of both peripheral inflammation and central sensitization. These results suggest a synergistic interaction between cacao polyphenols and pregabalin, offering enhanced anti-inflammatory and antinociceptive effects compared to pregabalin alone. The findings provide a basis for further preclinical investigations into the pharmacodynamic and pharmacokinetic profiles of this combination and highlight the potential of cacao extract as a safe, natural adjuvant in neuropathic pain management strategies.* **Keywords:** *Neuropathy, Pregabalin, Cacao, Inflammation, ERK.*

INTRODUCTION

Pain, both acute and chronic, remains a significant global health burden with substantial socioeconomic consequences. Acute postoperative pain, if inadequately managed, can evolve into chronic pain syndromes, impair recovery, prolong hospitalization, and reduce quality of life. On the other hand, neuropathic pain, resulting from nerve injury or dysfunction, is often persistent, poorly responsive to conventional analgesics, and associated with complex molecular alterations in the peripheral and central nervous systems. Despite the availability of pharmacologic agents such as opioids, NSAIDs, and anticonvulsants, their long-term use is limited by adverse effects including gastrointestinal complications, renal dysfunction, dependence, and tolerance. These limitations emphasize the urgent need for safer, effective, and targeted therapeutic strategies for pain management (Silva et al., 2022).

Natural products have long been a rich source of bioactive compounds with diverse pharmacological activities, including analgesic and anti-inflammatory properties. Cacao (*Theobroma cacao*), widely consumed as food and beverage, contains abundant polyphenolic compounds, particularly flavonoids such as epicatechin, catechin, and procyanidins (Fathani et al., 2024). These phytochemicals have been extensively studied for their antioxidant, vasodilatory, and neuroprotective effects. More recently, cacao-derived flavonoids have garnered attention for their potential analgesic effects through modulation of inflammatory mediators and intracellular signaling cascades implicated in pain perception and propagation (Silva et al. 2022; Pangestu et al., 2022)

Pain is mediated by intricate neuroimmune interactions and involves distinct but overlapping molecular pathways depending on its origin and duration (Zhao et al., 2021). In acute inflammatory pain, tumor necrosis

factor-alpha (TNF-α) is a central cytokine secreted by activated macrophages and glial cells (Jin et al., 2021). TNF-α contributes to peripheral sensitization by increasing nociceptor excitability and augmenting inflammatory responses at the injury site (H.-N. Li et al., 2021). Elevated TNF-α levels have been associated with heightened pain intensity and prolonged duration in both postoperative and inflammatory conditions (Zhao et al., 2021; Ammar et al., 2024).

Neuropathic pain, in contrast, involves both peripheral and central sensitization (Christin et al., 2023) and is marked by altered synaptic transmission and glial activation in the spinal cord and brain (Zhao et al., 2021). Key intracellular pathways, particularly the mitogen-activated protein kinase (MAPK) signaling cascade with a focus on extracellular signal-regulated kinase (ERK) are crucial in sustaining and intensifying neuropathic pain (Li et al., 2021; Ammar et al., 2024). MAPK activation contributes to hyperalgesia and allodynia by enhancing transcription of pro-inflammatory genes, increasing neuroinflammation, and modifying synaptic plasticity along pain pathways (Zhao et al., 2021). Inhibiting ERK pharmacologically has been shown to alleviate neuropathic pain symptoms in animal models, reinforcing its potential as a therapeutic target (Zhao et al., 2021; Jin et al., 2021).

Although previous research has examined the anti-inflammatory and analgesic effects of cacao, most studies have focused on either peripheral or central mechanisms independently, lacking a comprehensive evaluation across multiple pain modalities (Silva et al., 2022). There remains a scarcity of integrative investigations assessing the efficacy of cacao extract in diverse pain models that involve distinct molecular mechanisms (Pangestu et al., 2022). Furthermore, the potential application of cacao as a pre-emptive analgesic for acute pain and as an adjuvant therapy in neuropathic pain has not been thoroughly explored (Silva et al., 2022)

The present study aims to address this gap by investigating the multimodal analgesic properties of cacao extract in a chronic constriction injury (CCI) model of neuropathic pain (Edo et al., 2023). The study evaluates the synergistic effect of cacao extract administered in combination with pregabalin at full and reduced doses by measuring mechanical allodynia using von Frey testing, serum levels of tumor necrosis factor-alpha (TNF-α), and brain extracellular signal-regulated kinase (ERK) expression (Fathani et al., 2024,7]. This approach facilitates a focused analysis of peripheral and central mechanisms through which cacao may exert its analgesic effects. By targeting the TNF-α and ERK pathways, cacao extract holds promise as a novel phytotherapeutic agent with potential for enhancing neuropathic pain management (Ammar et al., 2024). The results from this investigation are expected to provide scientific rationale for developing cacao-based formulations as safe and effective adjuncts to conventional analgesics (Edo et al., 2023).

The main objective of this study is to assess the analgesic efficacy of cacao extract combined with pregabalin in a neuropathic pain model and to elucidate its underlying molecular mechanisms, particularly through modulation of TNF-α and ERK signaling pathways. This study seeks to establish cacao extract as a feasible adjuvant candidate in neuropathic pain therapy and contribute to expanding knowledge on plant-derived bioactive compounds in pain pharmacology (Ammar et al., 2024).

METHOD

This experimental study was conducted using a randomized post-test-only control group design to evaluate the effects of cacao extract as an adjuvant to pregabalin in an animal model of neuropathic pain. The study targeted two primary biomarkers, tumor necrosis factor-alpha (TNF-α) and extracellular signal-regulated kinase (ERK), within the same neuropathic framework. All protocols were approved by the Animal Care and Use Committee of the Faculty of Veterinary Medicine, Universitas Airlangga. The study adhered to institutional and international standards on ethical animal experimentation, with strict compliance to humane handling, anesthesia, and euthanasia practices.

Male mice (Mus musculus), aged between 8 and 12 weeks and weighing 25 to 30 grams, were utilized in both experimental protocols. Animals were acclimatized for seven days in a controlled laboratory environment, with ambient temperature maintained between 22 and 25 degrees Celsius and a 12-hour light/dark cycle. Mice were housed in standard cages, provided with free access to water and commercial rodent chow throughout the study. All animals were confirmed to be in healthy condition prior to the experimental procedures.

Cacao extract used in this study was obtained from fermented Theobroma cacao beans, processed through maceration using 70% ethanol to obtain a crude flavonoid-rich extract. The extract was filtered, evaporated under reduced pressure, and stored at 4°C in a desiccated container. Prior to administration, the extract was suspended in 1% carboxymethyl cellulose (CMC) to ensure homogeneity and appropriate delivery via oral gavage. The selected doses were 0.5 mg/g and 1 mg/g of body weight, determined based on prior pilot studies and literature evidence suggesting their bioactivity in modulating inflammatory pathways.

Neuropathic pain was induced using the chronic constriction injury (CCI) model, adapted from the standard Bennett and Xie procedure. Under general anesthesia induced with intraperitoneal injection of ketamine (75 mg/kg) and xylazine (10 mg/kg), the sciatic nerve of the right hind limb was exposed through a blunt dissection at the mid-thigh level. Three ligatures using 6-0 chromic catgut were loosely tied around the nerve with approximately 1 mm spacing between each knot, ensuring partial nerve constriction without complete occlusion of blood supply.

The animals were randomly assigned to four groups with six rats per group: CCI rats receiving placebo (CMC vehicle), CCI rats receiving pregabalin full dose, CCI rats receiving pregabalin full dose combined with cacao extract, and CCI rats receiving pregabalin half dose combined with cacao extract. Identical grouping was applied to the ERK MAPK study, with only the primary molecular endpoints differing. All treatments were administered orally once daily for seven consecutive days, starting from the first day after surgery.

Behavioral assessments were conducted on day 7 post-surgery using von Frey filament testing to evaluate mechanical allodynia as an indicator of neuropathic pain. Each animal was placed in a transparent acrylic chamber positioned on a wire mesh floor to allow filament application. Calibrated von Frey filaments ranging from 0.4 to 15 grams were applied to the plantar surface of the ipsilateral hind paw. A positive response was defined as a brisk paw withdrawal or licking behavior upon stimulation. The 50% paw withdrawal threshold was calculated using the up-and-down method, and lower thresholds were interpreted as increased pain sensitivity.

At the conclusion of the treatment period, animals were deeply anesthetized using ketamine/xylazine and euthanized by decapitation for tissue and blood collection. For the TNF-α analysis, blood samples were drawn via cardiac puncture, allowed to clot, and centrifuged at 3000 rpm for 10 minutes to obtain serum. The serum samples were then stored at –80°C prior to analysis (Li et al., 2022). TNF-α levels were measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit specific for rat TNF-α. All procedures followed the manufacturer's instructions, and absorbance was read at 450 nm using a microplate reader. Concentration values were expressed in pg/mL based on a standard curve (Abbasi et al., 2023).

For MAPK analysis, brain tissue was harvested immediately after sacrifice. The tissue was fixed in 10% buffered formalin, processed through graded alcohols, and embedded in paraffin. Four-micrometer sections were cut using a microtome and mounted on poly-L-lysine-coated slides (Li et al., 2022). Immunohistochemical staining was performed using antibodies against phosphorylated ERK1/2 to assess activation of intracellular signaling pathways. Following deparaffinization and antigen retrieval, sections were incubated with the primary antibody overnight at 4°C, followed by a secondary antibody and DAB substrate for visualization. Hematoxylin was used as a counterstain (Abbasi et al., 2023). The stained slides were analyzed under a light microscope, and the number of immunopositive cells per high-power field was quantified using ImageJ software.

All collected data were analyzed using SPSS or GraphPad Prism software. Behavioral and biochemical results were presented as mean ± standard deviation. Statistical comparisons between groups were performed using one-way analysis of variance (ANOVA), followed by Bonferroni's post hoc test when appropriate. A p-value of less than 0.05 was considered statistically significant. Graphs and tables were used to present comparative results in a clear and concise manner.

All procedures involving live animals were conducted in strict accordance with ethical standards established by the Animal Care and Use Committee of the Faculty of Veterinary Medicine, Universitas Airlangga (Number: 2.KEH.33.03.2025). The research protocols involving cacao extract as an adjuvant to pregabalin in neuropathic pain models were reviewed, approved, and declared ethically feasible. The study design ensured the use of the minimum number of animals necessary to achieve statistical relevance and incorporated all feasible measures to reduce pain and distress during the experimental process.

FINDINGS AND DISCUSSIONS Research Findings

This study aimed to evaluate the effect of cacao extract as an adjuvant to pregabalin therapy on inflammatory and cellular markers in a rat model of neuropathic pain induced by chronic constriction injury (CCI). Two primary outcome measures were investigated: serum levels of tumor necrosis factor-alpha (TNF-α) and brain expression of extracellular signal-regulated kinase (ERK)-positive cells. The study involved four experimental groups, the control group (K-) will receive placebo, treatment group 1 (K1) receives pregabalin 60mg/KgBW, treatment group 2 (K2) receives pregabalin 60mg/kgBW + cacao extract 1mg/gBW, and treatment group 3 (K3) receives pregabalin 30mg/kgBW + cacao extract 1mg/gBW.

Serum TNF-α levels were markedly elevated in the CCI + Placebo group, indicating a robust systemic inflammatory response following nerve injury. Pregabalin monotherapy resulted in a moderate reduction of TNF-α levels, while the combination therapies (pregabalin + cacao and pregabalin ½ dose + cacao) showed greater reductions, suggesting an additive anti-inflammatory effect. Serum TNF-α levels differed significantly among the groups, with the combination therapies showing highly significant reductions ($p < 0.01$) compared to the CCI + Placebo group (Table 1).

Table 1. Serum TNF-α Levels Across Experimental Groups (Mean ± SD)

Group	TNF-α (pg/mL) ± SD	Significance vs CCI + Placebo
Placebo	78.5 ± 3.6	–
Pregabalin	55.2 ± 2.9	*p < 0.05
Pregabalin + Cacao	30.1 ± 2.2	**p < 0.01
Pregabalin ½ dose + Cacao	35.4 ± 2.4	**p < 0.01

Note: Statistical analysis was performed using one-way ANOVA followed by Bonferroni post hoc test. Values are considered statistically significant at *p < 0.05.

Histological analysis of the brain tissue revealed similar trends in ERK expression, used as a marker of nociceptive cellular activation. The CCI + Placebo group exhibited a dense presence of ERK-positive cells, averaging 28.3 cells per high-power field (HPF), reflective of intense neuronal activation and central sensitization. Pregabalin monotherapy reduced ERK expression to 20.1 cells/HPF, while combination therapies further decreased the expression to 10.7 cells/HPF for pregabalin full dose + cacao and 12.9 cells/HPF for pregabalin ½ dose + cacao, suggesting effective modulation of central nociceptive pathways. ERK-positive cell counts were significantly attenuated by both combination treatments, with statistical significance confirmed at $p < 0.01$ (Table 2).

Table 2. ERK-Positive Cells per High Power Field (HPF) in Brain Tissue (Mean ± SD)

Treatment Group	ERK+ Cells/HPF ± SD	Significance vs CCI + Placebo
Placebo	28.3 ± 2.8	–
Pregabalin	20.1 ± 2.1	*p < 0.05
Pregabalin + Cacao	10.7 ± 1.4	**p < 0.01
Pregabalin ½ dose + Cacao	12.9 ± 1.6	**p < 0.01

Note: One-way ANOVA with Bonferroni post hoc test was used. Differences were considered significant at *p < 0.05.

Von Frey filament analysis showed that mechanical allodynia was most pronounced in the CCI + Placebo group. Pregabalin reduced pain sensitivity moderately, whereas both combination therapy groups significantly increased paw withdrawal thresholds. This pattern correlated with reductions in TNF-α and ERK levels, supporting the association between elevated inflammatory markers and heightened pain perception. Statistical analysis using ANOVA followed by Bonferroni's post hoc test revealed that the differences in TNFα and ERK levels across groups were statistically significant ($p < 0.05$). Pairwise comparisons indicated that pregabalin significantly reduced TNF-α levels compared to the placebo group. Notably, both combination therapy groups (pregabalin + cacao and pregabalin ½ dose + cacao) had significantly lower TNF-α levels than pregabalin monotherapy, supporting a synergistic interaction. Similar statistical significance was observed in

ERK expression among the groups, with the combination therapies outperforming pregabalin monotherapy in reducing cellular activation.

The reduction in TNF-α levels highlights the systemic anti-inflammatory potential of cacao polyphenols, possibly mediated through inhibition of NF-κB pathways and downregulation of proinflammatory cytokine synthesis. Pregabalin, primarily known for its binding to the α2δ subunit of voltage-gated calcium channels, may exert indirect anti-inflammatory effects via attenuation of neuronal excitability. The additive effect of cacao extract supports the hypothesis that polyphenolic compounds can enhance pregabalin's pharmacodynamic profile through complementary molecular targets.

In parallel, the observed decline in ERK-positive brain cells suggests reduced activation of intracellular signaling cascades implicated in chronic pain processing. ERK pathways have been associated with central sensitization and glial activation in neuropathic pain. The notable reduction in ERK expression in the combination therapy groups implies that cacao extract may exert neuroprotective effects by modulating intracellular signal transduction, thereby enhancing pregabalin's neuromodulatory efficacy.

Von Frey analysis further supported these biochemical findings. The CCI + Placebo group displayed the most severe mechanical allodynia, reflected in the lowest paw withdrawal thresholds. Pregabalin monotherapy improved withdrawal thresholds moderately, while both combination therapy groups achieved greater recovery, correlating with lower TNF-α and ERK levels. This suggests that elevated inflammatory and central sensitization markers are associated with more severe pain behaviors, and their suppression leads to functional improvement.

The integrated results from TNF-α and ERK analyses underscore the dual mechanism of cacao extract as both an anti-inflammatory and antinociceptive agent. When used as an adjuvant to pregabalin, cacao extract appears to enhance therapeutic outcomes by simultaneously attenuating peripheral inflammation and reducing central sensitization. These findings offer promising insights into the potential repositioning of cacao bioactive compounds in neuropathic pain management, particularly for enhancing the efficacy of existing pharmacologic agents like pregabalin.

DISCUSSION Synergistic Anti-inflammatory and Antinociceptive Effects of Cacao and Pregabalin

The present study highlights the therapeutic potential of combining cacao extract with pregabalin in the management of neuropathic pain, particularly in modulating inflammatory and nociceptive cellular responses. The significant reduction in serum TNF-α levels and brain ERK expression observed in the combination therapy groups compared to pregabalin monotherapy suggests a synergistic interaction between these two agents. This finding is particularly relevant given the limitations of pregabalin monotherapy, including dose-dependent side effects and incomplete pain relief in a subset of patients (Silva et al., 2022). Cacao extract, rich in polyphenols such as epicatechin and catechin, is known for its anti-inflammatory and antioxidant properties. These compounds may act by inhibiting nuclear factor kappa B (NF-κB) activation, leading to downregulation of pro-inflammatory cytokines, including TNF-α (Pangestu et al., 2022). Pregabalin, while not a direct anti-inflammatory agent, may exert secondary immunomodulatory effects via suppression of excitatory neurotransmission, which indirectly attenuates cytokine production (Silva et al., 2022). The observed additive effect of combining cacao with pregabalin suggests a complementary mechanism where cacao targets upstream inflammatory signaling, while pregabalin modulates downstream neuronal hyperexcitability.

Modulation of TNF-α as a Biomarker of Systemic Inflammation

Tumor necrosis factor-alpha is a key mediator in the pathophysiology of neuropathic pain. Its upregulation following nerve injury contributes to sensitization of nociceptors, activation of glial cells, and propagation of pain signals both peripherally and centrally. In this study, TNF-α levels were significantly elevated in the CCI + Placebo group, consistent with the systemic inflammatory response associated with nerve ligation. Pregabalin reduced TNF-α levels moderately, while the combination therapies significantly suppressed TNFα levels beyond that of pregabalin monotherapy, supporting a synergistic anti-inflammatory effect (Ribeiro et al., 2023).

The reduction in TNF-α levels in the cacao-treated groups may also reflect the suppression of reactive oxygen species and inhibition of inducible nitric oxide synthase (iNOS), both of which are downstream targets of

NF-κB signaling (Rodríguez-Ramiro et al., 2013). Moreover, cacao polyphenols may influence gut-brain axis signaling, modulating systemic inflammation through improved gut barrier integrity and microbiota balance an emerging area in neuroinflammation research (Shen et al., 2022).

Inhibition of ERK Pathways in Brain Neurons

The extracellular signal-regulated kinase (ERK) pathway plays a critical role in intracellular processes associated with pain perception, synaptic plasticity, and neuroinflammation. Increased ERK expression in brain neurons, as observed in the CCI + Placebo group, is a hallmark of central sensitization (De Feo et al., 2020). This study found that pregabalin monotherapy suppressed ERK-positive cell counts moderately, while both combination therapies (pregabalin + cacao and pregabalin ½ dose + cacao) resulted in a more significant reduction, suggesting a potential synergistic interaction.

These results indicate that cacao extract may confer neuroprotective effects by inhibiting ERK phosphorylation, thereby reducing downstream transcriptional activation of pro-nociceptive genes and inflammatory mediators in brain neurons and glial cells. The observed synergistic effect strengthens the hypothesis that cacao extract enhances the efficacy of pregabalin by concurrently targeting different components of central sensitization pathways.

This finding aligns with prior studies indicating that ERK inhibition mitigates neuropathic pain behaviors. The enhanced reduction in ERK expression seen in the combination therapy groups supports the concept that cacao may act as a biological enhancer of pregabalin, promoting a synergistic effect on central pain signaling targets (De Feo et al., 2020).

Integration with Behavioral Outcomes

Von Frey filament testing in this study demonstrated a clear correlation between behavioral and biochemical findings. Rats receiving pregabalin in combination with cacao extract, whether at full or half dose, exhibited the greatest improvements in mechanical allodynia, as reflected in significantly higher paw withdrawal thresholds compared to the placebo and pregabalin monotherapy groups (Alothman et al., 2024). This pattern aligns with the observed reductions in serum TNF-α levels and brain ERK expression, supporting a synergistic analgesic effect of the combination therapies.

This alignment between behavioral, histological, and biochemical outcomes enhances the internal validity of the findings and supports the translational potential of this therapeutic approach. The observed improvement likely stems from the attenuation of both peripheral and central sensitization mechanisms. Pregabalin acts on α2δ subunits of voltage-gated calcium channels to reduce excitatory neurotransmitter release, contributing to analgesia (Alothman et al., 2024). Meanwhile, cacao's polyphenolic components are known to reduce glial activation and oxidative stress, thereby modulating the neuroinflammatory environment. These effects may disrupt the positive feedback loop of chronic pain amplification, ultimately facilitating improved functional recovery (Alothman et al., 2024). **Clinical Implications and Relevance**

The combination of cacao extract and pregabalin offers promising clinical implications for treating neuropathic pain, particularly in chronic conditions such as diabetic neuropathy, postherpetic neuralgia, and chemotherapy-induced peripheral neuropathy (Castro et al., 2020). Cacao's natural origin, favorable safety profile, and accessibility suggest its potential as an adjuvant therapy to reduce required pregabalin doses, thereby minimizing adverse effects such as dizziness, sedation, and weight gain (Shokri et al., 2021).

This integrative strategy reflects the growing paradigm of phytopharmacologic modulation, wherein natural bioactive compounds are utilized to enhance standard pharmacological treatments. Cacao polyphenols, in particular, have demonstrated anti-inflammatory and antioxidant effects that could modulate pain signaling pathways and glial activity (Castro et al., 2020). Moreover, pregabalin remains a first-line pharmacologic treatment in neuropathic pain due to its proven efficacy (Mandra et al., 2024). The synergy between these agents holds translational potential, especially for patients who experience suboptimal responses to monotherapy or have contraindications to high-dose pregabalin.

Limitations and Future Directions

While the current findings are promising, several limitations should be acknowledged. The small sample size and absence of comprehensive behavioral scoring beyond von Frey analysis may limit the generalizability of the results. Although TNF-α and ERK are important markers of peripheral and central sensitization,

incorporating additional cytokines such as IL-6, IL-1β, and neurotrophic factors like BDNF could provide a more complete mechanistic understanding (Alothman et al., 2024).

Future studies should focus on the pharmacokinetics of cacao polyphenols in the presence of pregabalin, their long-term effects, and the potential risk of developing pharmacological tolerance. In-depth analyses using electrophysiological recordings and molecular techniques, such as Western blotting for phosphorylated ERK isoforms, could significantly improve mechanistic insight (Kawakami et al., 2021).

Further preclinical research is essential to validate the efficacy and safety of cacao as an adjunctive agent in neuropathic pain models. To our knowledge, this is the first study to investigate the combined effect of cacao extract and pregabalin on both systemic inflammation and brain ERK signaling in a neuropathic pain model. The observed synergistic reduction of TNF-α levels and ERK activation suggests a novel therapeutic approach for chronic pain management (Alothman et al., 2024). This research contributes to the expanding domain of integrative neurotherapeutics by bridging phytopharmacology with conventional neuropharmacological strategies.

CONCLUSIONS

This study demonstrates that cacao extract, when used as an adjuvant to pregabalin, significantly enhances anti-inflammatory and antinociceptive effects in a rat model of neuropathic pain. The combination therapies resulted in substantial reductions in serum TNF-α levels and brain ERK expression, correlating with improved mechanical allodynia as measured by von Frey testing. These findings support the potential role of cacao extract in enhancing pregabalin efficacy through complementary mechanisms targeting peripheral inflammation and central sensitization. Further preclinical and pharmacokinetic studies are warranted to explore the translational potential of this combination strategy in neuropathic pain management.

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