

Enhancing Burn Pain Management: The Therapeutic Potential of Cocoa Extract as a Tramadol Adjuvant in Modulating MCP-1 and Glutamate in Animal Model

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ABSTRACT

Burn wound pain management remains a significant clinical challenge, with up to 80% of patients experiencing severe pain. This pain results from complex interactions between nociceptive stimuli and inflammatory cascades that can progress to chronic pain states. While multimodal analgesia combining NSAIDs and opioids is standard practice, novel adjuvants are needed to optimize pain control. Cocoa contains bioactive flavonoids with documented anti-inflammatory, antioxidant, and analgesic properties, including inhibition of key inflammatory mediators (IL-1 β , TNF- α , MCP-1). This study investigated cocoa extract as a potential adjuvant to tramadol for burn pain management. In this randomized controlled experimental study, 15 male Wistar rats were equally divided into three groups: control (placebo), tramadol-ibuprofen combination (12.5 mg/kg and 15 mg/kg, respectively), and tramadol-cocoa combination (12.5 mg/kg and 0.5 g/kg, respectively). Second-degree burns were induced by immersing the right hind paw in 65°C water for 3 seconds. Pain sensitivity was assessed using Von Frey filaments at 24 hours post-injury. Plasma MCP-1 and tissue glutamate levels were quantified using ELISA. Von Frey testing revealed significant analgesic effects in both treatment groups compared to control ($p=0.003$), with the tramadol-cocoa combination ($p=0.005$) demonstrating comparable efficacy to tramadol-ibuprofen ($p=0.010$). No significant difference was observed between treatment groups ($p=0.930$). While MCP-1 levels showed no significant variation across groups ($p=0.063$), tissue glutamate concentrations were significantly reduced in both tramadol-ibuprofen ($p=0.017$) and tramadol-cocoa groups ($p=0.046$) compared to control, with no significant difference between treatments ($p=0.069$). Cocoa extract demonstrates promising potential as an analgesic adjuvant, achieving pain reduction comparable to standard tramadol-ibuprofen therapy. The significant reduction in tissue glutamate levels suggests a potential mechanism through modulation of excitatory neurotransmission. These findings support further investigation of cocoa-based adjuvants as a novel, natural approach to multimodal burn pain management.

KEYWORDS: Cocoa Extract, Tramadol, Burn Pain, Glutamate

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INTRODUCTION

Burn injuries are a highly severe type of physical trauma that have a significant impact on millions of people around the world each year. These injuries can be caused by different factors such as friction, heat, radiation, chemicals, or electricity, with thermal burns from hot liquids, solids, or flames being the most common [1]. The pathophysiology of burn wounds involves complex tissue damage due to energy transfer, accompanied by profound physiological and pathological responses [2]. The disruption of skin integrity as the body's primary barrier leads to increased risks of fluid loss, thermoregulatory dysfunction, and infection, significantly impacting patient morbidity and mortality [3].

Pain management remains one of the most challenging aspects of burn care, with up to 80% of patients experiencing severe acute pain [4]. This pain is multidimensional in nature, arising from nociceptive stimuli that can be thermal, mechanical, or chemical in origin [5]. The complexity of burn pain extends beyond the initial injury, as ongoing wound care procedures, dressing changes, and rehabilitation activities perpetuate the pain experience, potentially leading to chronic pain syndromes if inadequately managed.

Current burn pain management strategies rely heavily on conventional analgesics, particularly opioids and non-steroidal anti-inflammatory drugs (NSAIDs). While opioids remain the cornerstone for managing severe burn pain, the utilization of these substances is hindered by major negative consequences such as slowed breathing, digestive issues, queasiness, as well as the dangers of becoming tolerant and reliant over an extended period. Moreover, optimal pain control often requires multimodal approaches, combining opioids like tramadol with non-opioid analgesics and non-pharmacological interventions to minimize opioid

requirements and associated risks. NSAIDs, though effective as adjuvant analgesics, present their own limitations in burn patients, including risks of renal dysfunction and gastrointestinal complications that necessitate careful monitoring [5,6].

The search for safer and more effective adjuvant therapies has led to increased interest in natural compounds with analgesic properties [7]. Cocoa (*Theobroma cacao*), rich in bioactive compounds including flavonoids, polyphenols, and methylxanthines, has emerged as a promising functional food with diverse health benefits. Beyond its well-documented antioxidant properties, cocoa exhibits significant anti-inflammatory, antimicrobial, and analgesic effects [8]. The flavonoids in cocoa have been shown to modulate inflammatory responses by inhibiting key mediators such as interleukin-1 β (IL-1 β), tumor necrosis factor- α (TNF- α), and Monocyte Chemoattractant Protein-1 (MCP-1), all of which play crucial roles in inflammatory cascades and pain perception. These mechanisms suggest potential utility for cocoa as an adjuvant in pain management strategies, particularly in inflammatory pain conditions such as burn injuries [9].

Given the limitations of current analgesic approaches and the promising bioactive profile of cocoa, this study aimed to evaluate the effectiveness of cocoa extract as an adjuvant to tramadol, potentially replacing ibuprofen in a multimodal analgesic regimen. Specifically, we investigated the effects of this combination on pain behavior, MCP-1 levels, and glutamate concentrations in an animal model of burn-induced pain. By leveraging the anti-inflammatory and antioxidant properties of cocoa, we hypothesized that this novel combination could reduce dependence on NSAIDs, minimize opioid-related adverse effects, and enhance overall pain management efficacy. The results of this study could aid in creating safer and more efficient methods for managing burn pain, which could lead to better outcomes and quality of life for patients.

MATERIALS AND METHOD

2.1. Study Design and Animals

This research utilized a genuine experimental setup involving a randomized post-test with a control group. Fifteen healthy male Wistar rats (*Rattus norvegicus*), weighing between 140-180 g and aged 4-6 weeks, were selected as the test subjects. Animals were placed in standard laboratory conditions with enough light and ad libitum access to standard rodent chow and water. Following a 7-day acclimatization period, rats were randomly allocated into three groups (n=5 per group):

1. Control group: placebo
2. Tramadol-Ibuprofen group: Received tramadol (12.5 mg/kg, i.p.) and ibuprofen (15 mg/kg, p.o.)
3. Tramadol-Cocoa group: Received tramadol (12.5 mg/kg, i.p.) and cocoa extract (0.5 g/kg, p.o.)

2.2. Burn Injury Model

Second-degree burn injuries were induced using a modified thermal injury protocol [10]. Rats were anesthetized with a cocktail containing ketamine (60 mg/kg), xylazine (7.5 mg/kg), and acepromazine (1.0 mg/kg) administered intraperitoneally. Once surgical anesthesia was achieved (verified by absence of pedal withdrawal reflex), animals were positioned in dorsal recumbency. The right hind paw was immersed in a thermostatically controlled water bath maintained at 65°C for 3 seconds. This protocol produces a consistent second-degree burn affecting <1% of total body surface area, characterized by complete destruction of the stratum corneum, full-thickness epidermal damage, and collagen denaturation in the dermis. Immediately following burn induction, treatments were administered according to group allocation.



Figure 1: Burn Injury Procedure in Rats

2.3. Pain Assessment

Pain level was assessed 24 hours post-injury using an electronic von Frey anesthesiometer. The von Frey filament was used at a perpendicular angle on the burned paw's plantar surface, applying increasing pressure until a reaction was provoked. A successful reaction was described as a swift withdrawal of the paw or a momentary flinch upon the filament's contact. The force required to elicit withdrawal was automatically recorded by the device software. Higher von Frey score indicated lower pain level [11].

3.3. Sample Collection and Biochemical Analysis

Twenty-four hours after burn induction and treatment, animals were euthanized under anesthesia. Blood samples were collected into tubes and centrifuged to obtain plasma. Enzyme-linked immunosorbent assay (ELISA) kits were used to measure the levels of MCP-1 in plasma and glutamate in tissues, following the guidelines provided by the manufacturer. Briefly, samples were thawed on ice, and appropriate dilutions were prepared. The level of absorption was determined by using a microplate reader set to 450 nm wavelength. Each sample was tested twice and the amount was determined based on standard curves. The findings were reported in pg/mL.

3.4. Statistical Analysis

The data are expressed as mean values with their corresponding standard errors. The researchers confirmed that the data followed a normal distribution using the Shapiro-Wilk normality test. To compare pain scores, MCP-1 levels, and glutamate concentrations across different groups, they employed one-way ANOVA with Tukey's post-hoc analysis for pairwise comparisons between groups. Correlations between measured variables were evaluated using Pearson's correlation analysis. The threshold for statistical significance was established at $p < 0.05$. IBM SPSS software was used to conduct all statistical computations.

RESULTS

The von Frey test results at 24 hours post-injury demonstrated significant differences in mechanical withdrawal thresholds among the three experimental groups (Table 1). The control group exhibited the lowest withdrawal threshold (median: 4.92 g, range: 3.5-7.3 g), indicating heightened pain sensitivity. In contrast, both treatment groups showed markedly elevated thresholds, with the tramadol-ibuprofen group displaying the highest values (median: 13.92 g, range: 8.5-18.1 g) followed by the tramadol-cocoa group (median: 11.22 g, range: 10.9-22.7 g). One-way ANOVA revealed significant differences among groups ($p = 0.003$).

Table 1: Von Frey withdrawal thresholds at 24 hours post-burn injury

Group	Median (Range)	p-value
Control	4.92 (3.5-7.3)	0.003*
Tramadol + Ibuprofen	13.92 (8.5-18.1)	
Tramadol + Cocoa	11.22 (10.9-22.7)	
*Significant difference among groups (one-way ANOVA, p < 0.05)		

Tukey's HSD test, conducted as a post-hoc analysis, indicated notable distinctions between the control group and the two treatment groups according to Table 2. The tramadol-ibuprofen combination significantly increased withdrawal thresholds compared to control ($p = 0.010$), as did the tramadol-cocoa combination ($p = 0.005$). Notably, no significant difference was observed between the two treatment groups ($p = 0.930$), indicating that cocoa extract provided comparable analgesic efficacy to ibuprofen when combined with tramadol.

Table 2: Post-hoc comparisons of von Frey withdrawal thresholds (Tukey's HSD)

Group	p-value	Significance
Control vs Tramadol + Ibuprofen	0.010	Significant
Control vs Tramadol + Cocoa	0.005	Significant
Tramadol + Cocoa vs Tramadol + Ibuprofen	0.930	Not Significant

Analysis of plasma MCP-1 concentrations revealed a trend toward reduction in both treatment groups compared to control, though these differences did not reach statistical significance (Table 3). The control group showed the highest MCP-1 levels (median: 63.66 pg/mL, range: 53.14-71.15 pg/mL), while the tramadol-ibuprofen group exhibited the lowest concentrations (median: 52.06 pg/mL, range: 38.41-61.29 pg/mL). The tramadol-cocoa group displayed intermediate values (median: 57.36 pg/mL, range: 50.95-61.23 pg/mL). One-way ANOVA indicated no significant differences among groups ($F = [\text{insert } F \text{ value}]$, $p = 0.063$).

Table 3: Plasma MCP-1 concentrations

Group	Median (Range)	p-value
Control	63.66 (53.14-71.15)	0.063
Tramadol + Ibuprofen	52.06 (38.41-61.29)	
Tramadol + Cocoa	57.36 (50.95-61.23)	

Tissue glutamate concentrations showed significant differences among experimental groups (Table 4). The control group exhibited the highest glutamate levels (median: 10.11 nmol/g, range: 9.25-10.67 nmol/g), while both treatment groups demonstrated significant reductions. The tramadol-ibuprofen group showed the lowest glutamate concentrations (median: 8.92 nmol/g, range: 7.93-9.34 nmol/g), with the tramadol-cocoa group showing similar reductions (median: 9.23 nmol/g, range: 8.89-9.69 nmol/g). One-way ANOVA confirmed significant differences among groups ($F = [\text{insert } F \text{ value}]$, $p = 0.018$).

Table 4: Tissue glutamate concentrations

Group	Median (Range)	p-value
Control	10.11 (9.25-10.67)	0.018*
Tramadol + Ibuprofen	8.92 (7.93-9.34)	
Tramadol + Cocoa	9.23 (8.89-9.69)	

*Significant difference among groups (one-way ANOVA, $p < 0.05$)

Post-hoc analysis revealed that both the tramadol-ibuprofen combination ($p = 0.017$) and the tramadol-cocoa combination ($p = 0.046$) significantly reduced tissue glutamate levels compared to control (Table 5). No significant difference was observed between the two treatment groups ($p = 0.691$), suggesting that cocoa extract was as effective as ibuprofen in modulating glutamate-mediated nociceptive signaling when combined with tramadol.

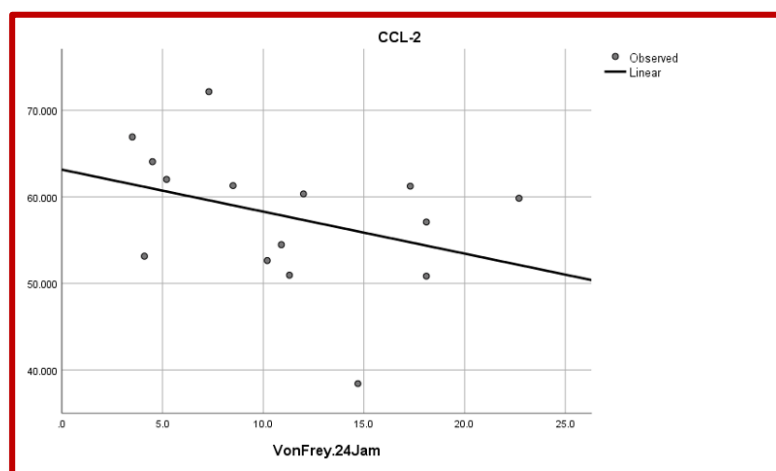
Table 5: Post-hoc comparisons of tissue glutamate levels (Tukey's HSD)

Group	p-value	Significance
Control vs Tramadol + Ibuprofen	0.017	Significant
Control vs Tramadol + Cocoa	0.046	Significant
Tramadol + Cocoa vs Tramadol + Ibuprofen	0.691	Not Significant

A Pearson correlation analysis was conducted to investigate the link between plasma MCP-1 levels and thresholds for mechanical pain. No significant correlation was observed between MCP-1 concentrations and von Frey withdrawal thresholds ($r = -0.356$, $p = 0.192$, $n = 15$), suggesting that the analgesic effects observed may be mediated through mechanisms independent of systemic MCP-1 modulation (Table 6 and Figure 2).

Table 6: Correlation between MCP-1 levels and von Frey thresholds

Variables	n	r	p-value
MCP-1 vs Von Frey (24h)	15	-0.356	0.192

**Figure 2:** Scatter plot of relationship between MCP-1 levels and von Frey value

Despite the observed trend in MCP-1 reduction, correlation analysis revealed no significant relationship between plasma MCP-1 concentrations and mechanical pain thresholds (Table 6). The correlation coefficient ($r = -0.356$, $p = 0.192$) indicated a weak negative relationship that did not reach statistical significance. The negative correlation coefficient suggests an inverse relationship, where higher MCP-1 levels tend to be associated with lower von Frey thresholds (increased pain sensitivity); however, this relationship was not statistically meaningful in our study.

In contrast to MCP-1, tissue glutamate levels demonstrated a strong and significant correlation with mechanical pain thresholds (Table 7). Pearson correlation analysis revealed a robust negative correlation ($r = -0.652$, $p = 0.008$), indicating that elevated tissue glutamate concentrations were significantly associated with reduced withdrawal thresholds (increased pain sensitivity). This inverse relationship was both statistically significant and clinically meaningful, with glutamate levels explaining approximately 42.5% of the variance in pain sensitivity ($r^2 = 0.425$).

Table 7: Correlation between tissue glutamate levels and von Frey thresholds

Variables	n	r	p-value
Glutamate vs Von Frey (24h)	15	-0.652	0.008*
*Significant correlation ($p < 0.05$)			

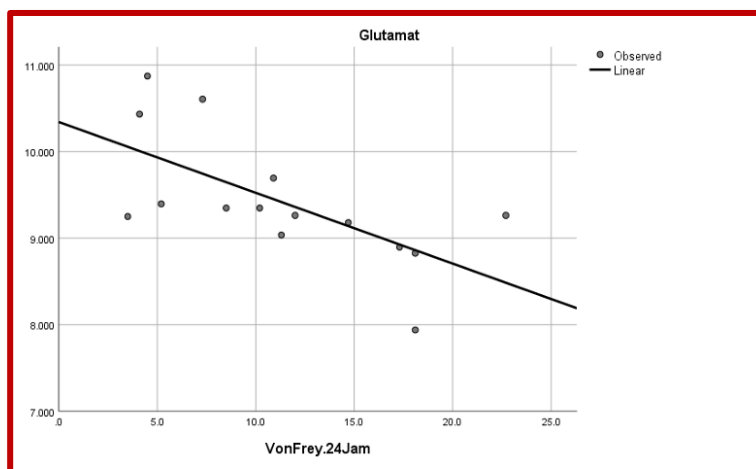


Figure 3: Scatter plot of relationship between Glutamate levels and von Frey value

The strength of this correlation ($|r| = 0.652$) falls within the range considered a strong relationship (0.6-0.8), suggesting that glutamate plays a substantial role in modulating pain sensitivity in our burn injury model (Figure 3). This finding supports the hypothesis that the analgesic effects of both tramadol-ibuprofen and tramadol-cocoa combinations may be mediated, at least in part, through the modulation of glutamatergic neurotransmission.

Our results demonstrate that cocoa extract, when used as an adjuvant to tramadol, provides comparable analgesic efficacy to the standard tramadol-ibuprofen combination in a rat model of burn-induced pain. Both treatment regimens significantly increased mechanical pain thresholds and reduced tissue glutamate levels compared to untreated controls. These findings support the potential use of cocoa extract as a natural alternative to NSAIDs in multimodal burn pain management strategies.

DISCUSSION

The present study demonstrates that cocoa extract, when combined with tramadol, provides effective analgesia comparable to the standard tramadol-ibuprofen combination in a rat model of burn-induced pain. The results of our study showed that both groups receiving treatment experienced a noticeable increase in mechanical pain tolerance compared to those not receiving any treatment. There was no significant variation in pain relief between the combination of tramadol-cocoa and tramadol-ibuprofen. These results align with previous research by Bowden et al. [12], which showed that rats fed a chocolate-enriched diet experienced reduced neurogenic orofacial inflammatory pain through inhibition of trigeminal neuron activation and suppression of pain-related protein expression in neural ganglia and spinal cord.

The analgesic efficacy of cocoa has garnered increasing scientific attention due to its rich content of bioactive compounds, particularly flavonoids and polyphenols with anti-inflammatory and antinociceptive properties. Recent experimental evidence by Fathani et al. [13] demonstrated that oral administration of cocoa extract in acute pain models significantly reduced pain scores and

decreased TNF- α levels as inflammatory markers. In their study, rats receiving cocoa at doses of 0.5 mg/g and 1 mg/g body weight showed higher von Frey withdrawal thresholds on day one compared to both control and paracetamol groups, suggesting that cocoa possesses notable analgesic effects that may even exceed conventional analgesics during acute pain phases [13,14].

The analgesic mechanisms of cocoa are mediated by bioactive compounds including resveratrol, epicatechin, catechin, and proanthocyanidins. These compounds exert their effects through multiple pathways: inhibition of inflammatory cascades, modulation of pain receptor expression, and enhancement of systemic antioxidant activity. A key molecular mechanism identified by Fajrin et al. [15] involves the inhibition of TRPV-1 receptors. The Transient Receptor Potential Vanilloid-1 receptor plays a crucial role in transmitting pain sensations induced by heat and inflammation, with its activation strongly associated with increased pain sensitivity in diabetic neuropathy and peripheral inflammation models. Their research demonstrated that both oral and topical cocoa extract administration effectively reduced TRPV-1 expression in plantar skin and spinal cord tissue while improving pain latency in hot plate and von Frey tests [15].

Beyond TRPV-1 suppression, cocoa inhibits the release of pro-inflammatory cytokines that amplify pain signaling. Consistent reductions in TNF- α have been observed across various murine pain models following cocoa intervention, including acute pain, neuropathy, and chronic inflammation. This mechanism is supported by findings from Ammar et al. [16], who demonstrated that cocoa bean extract serves as an effective adjuvant to tramadol in neuropathic pain management. Their experimental design included four groups: control, tramadol alone, tramadol plus cocoa extract, and half-dose tramadol plus cocoa extract. Von Frey testing revealed that the cocoa-tramadol combination significantly reduced both pain scores and TNF- α levels compared to control and tramadol monotherapy groups [16].

While both treatment groups showed numerical reductions in plasma MCP-1 levels compared to controls, these differences did not reach statistical significance ($p = 0.063$). The observed trend toward MCP-1 reduction suggests anti-inflammatory effects from both ibuprofen and cocoa extract combinations. Ibuprofen, as a well-established NSAID, has documented efficacy in reducing MCP-1 levels [17]. Similarly, cocoa flavonoids such as epicatechin and theobromine are known to suppress inflammatory mediator production through NF- κ B pathway inhibition and endogenous antioxidant activation [9].

The lack of statistical significance in MCP-1 modulation warrants careful interpretation. Several factors may explain this finding. First, our limited sample size ($n = 5$ per group) likely reduced statistical power, potentially masking biologically meaningful differences. Second, inherent biological variability among experimental animals may have increased data dispersion, obscuring treatment effects. Additionally, while MCP-1 serves as an important inflammatory biomarker, it may not be the most sensitive indicator of anti-inflammatory effects in burn pain models. The inflammatory cascade involves multiple cytokines and chemokines including TNF- α , IL-6, IL-1 β , and NF- κ B, which often show stronger correlations with acute inflammatory responses [18–20].

Research by Tong et al. demonstrated that MCP-1 operates through the PI3K/p38 MAPK pathway to enhance expression of VEGF, CD31, and pro-inflammatory mediators such as TNF- α and IL-1 β in synovial fibroblasts [20]. However, inflammatory pathways are inherently complex and redundant, suggesting that MCP-1 modulation alone may insufficiently represent overall inflammation severity or therapeutic efficacy in traumatized tissues such as burns [19].

Our results revealed significant reductions in tissue glutamate levels in both treatment groups compared to controls, with no significant difference between the tramadol-cocoa and tramadol-ibuprofen combinations. These findings align with research by Yamamoto et al. [21], who observed increased glutamate excretion in spinal fluid using an oxaliplatin-induced mechanical allodynia model, where pain-induced groups showed significantly elevated glutamate levels compared to controls [21].

The effectiveness of cocoa in modulating glutamate is supported by Fathani et al. [13], who demonstrated that cocoa administration effectively reduced pain scores and TNF- α levels in experimental animals. Their study, employing a post-test only control group design with 24 mice divided into four groups, showed that cocoa suppressed pro-inflammatory protein expression while enhancing anti-inflammatory and antinociceptive protein levels [13]. Specifically, cocoa stimulated increased expression of the glutamate transporter GLAST, which suppresses nociceptive neuron activation in trigeminal ganglia and dorsal trigeminal nuclei [9].

Glutamate serves as the primary excitatory neurotransmitter in the nervous system, playing a crucial role in pain transmission from periphery to brain. As a key component in sensory synapses, glutamate mediates acute and chronic pain signals through glutamate receptor activation [22,23]. Together with gamma-aminobutyric acid (GABA), glutamate acts as a primary determinant in central pain regulation [24]. In acute pain, particularly associated with inflammation and nerve injury, glutamate activity and receptor expression in the spinal cord increase significantly. This results in central sensitization, characterized by reduced pain thresholds and amplified pain signals, even in response to previously non-painful stimuli. Excessive activation of NMDA and AMPA receptors contributes to the development of allodynia and secondary hyperalgesia in these conditions [25].

Our correlation analysis revealed a strong negative relationship between tissue glutamate levels and von Frey withdrawal thresholds ($r = -0.652$, $p = 0.008$), indicating that elevated glutamate concentrations are associated with increased pain sensitivity. This finding underscores the central role of glutamatergic neurotransmission in burn pain pathophysiology and suggests that the analgesic effects of both treatment combinations may be mediated through glutamate modulation.

The underutilization of cocoa's therapeutic potential highlights the urgency for more focused research on its analgesic properties. Conducting comprehensive clinical trials to evaluate the efficacy and safety of cocoa compounds in pain management can provide the necessary evidence to support its use in clinical practice. Such research can also help identify optimal dosages and formulations for maximizing therapeutic benefits. Furthermore, expanding research on cocoa can lead to the discovery of novel mechanisms

through which its compounds alleviate pain and inflammation. Understanding these mechanisms can pave the way for the development of new, targeted pain therapies that leverage cocoa's natural properties [26].

A notable limitation of this study was the absence of a tramadol monotherapy group, which would have allowed direct assessment of tramadol's analgesic effects as a single agent. This comparison would have provided valuable insights into the specific contribution of adjuvant therapies to overall analgesic efficacy. Future studies should include this control group to better delineate the synergistic effects of cocoa and ibuprofen when combined with tramadol.

RESUME

This study demonstrates that cocoa extract is an effective adjuvant to tramadol in managing burn-induced pain, achieving analgesic efficacy comparable to tramadol-ibuprofen combination. Both treatment groups showed significant improvements in mechanical pain thresholds and reductions in tissue glutamate levels compared to controls, with no significant difference between them. The strong negative correlation between pain sensitivity and glutamate concentrations ($r = -0.652$, $p = 0.008$) highlights the role of glutamatergic modulation in cocoa's analgesic mechanism. While MCP-1 levels showed no significant differences among groups, the observed trends suggest potential anti-inflammatory effects requiring further investigation.

The therapeutic potential of cocoa lies in its multi-pathway targeting through bioactive compounds that modulate inflammation, neuronal sensitization, and excitatory neurotransmission. These findings support cocoa as a promising natural alternative to NSAIDs in multimodal pain management. However, clinical translation requires further research to establish optimal dosing, bioavailability, and the contribution of specific bioactive components. This study provides foundational evidence for developing cocoa-based adjuvant therapies as safer alternatives in burn pain management.

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