Journal of Carcinogenesis
Covering Genesis to Therapeutics

Journal of Carcinogenesis, ISSN: 1477-3163
2025; Vol 24: Issue 2s, https://carcinogenesis.com/

Pharmacological Evaluation of CB2 Receptor Modulator in the Treatment of Neuropathic Pain

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ABSTRACT

Neuropathic pain (NP), a complex and incapacitating chronic condition, significantly affects patients' quality of life and poses a significant challenge to healthcare systems across the world. Through the CB1 and CB2 pathways, cannabinoids successfully lessen hyperalgesia and allodynia in animal models of neuropathic pain. Numerous cannabinoids, such as synthetic endocannabinoids, cannabinoid agonists (CB1), cannabinoid receptor antagonists (CB2), and endocannabinoid modulators, have been shown in animal experiments to lessen neuropathic pain behaviour. Animal models of traumatic nerve damage, including chronic constriction injury, partial nerve ligation, and spinal nerve ligation models, as well as neuropathy models brought on by metabolic issues or toxins, such as streptozotocin- and chemotherapy-induced neuropathy, have shown effectiveness. In this study, we examine the pharmacological and molecular impacts of cannabinoid receptor agonists on rats' neuropathic pain caused by paclitaxel. A range of biochemical indicators, including as CRP, and catalase activity, were assessed in close proximity to behavioural responses using the acetone drop, pin prick, and tail flick tests. The findings demonstrated that CB2 modulation eased pain while lowering pro-inflammatory cytokines and oxidative stress. These results show that cannabinoid receptor agonists are a viable treatment option for chemotherapy-induced peripheral neuropathy and have the potential to reduce neuropathic pain.

Keywords: *Neuropathic pain, CB2 receptor, therapeutic, endocannabinoid, paclitaxel*

How to Cite: Amit Kumar Bhatt, Krishana Kumar Sharma, (2025) Pharmacological Evaluation of CB2 Receptor Modulator in the Treatment of Neuropathic Pain, *Journal of Carcinogenesis*, *Vol.24, No.2s*, 867-885

1. INTRODUCTION

The first indication that CB2 receptor pathways have a role in regulating chronic pain states was indirect. The systemic and intraplantar injection of palmitoylethanolamide (PEA), an endogenous fatty acid amide, produces antinociception that is blocked by SR144528, a CB2-receptor-selective antagonist(Calignano et al., 2001, 1998). When given orally, PEA reduced inflammatory hyperalgesia and oedema by inhibiting mast cell degranulation and the synthesis of inflammatory mediators that activate nociceptors(Javaid et al., 2024). Since PEA does not bind to CB2 receptors, many investigations have shown that it is not a direct agonist at these receptors (De Petrocellis et al., 2002; Griffin et al., 2000; Lo Verme et al., 2005; Showalter et al., 1996).

The subsequent development and evaluation of CB2-selective agonists, such as HU308, AM1241, JWH-133, and GW405833 (L768242), has provided direct evidence that activation of CB2 has antinociceptive effects in chronic pain settings (Kumar Sharma et al., 2023; Singh et al., 2022). Importantly, CB2-selective agonists like HU308 and AM1241 do not produce centrally mediated side effects such hypoactivity, hypothermia, and catalepsy, in contrast to CB1 receptor activators (Hanuš et al., 1999; Malan et al., 2001). These results support the hypothesis that cannabinoid agonists (CB2 agonists) are unlikely to be intoxicated or addicted. Few cannabinoid receptors were discovered in the brains of naïve animals by (Buckley et al., 2000; Galiègue et al., 1995; Munro et al., 1993; Zimmer et al., 1999).This finding is consistent with the absence of CNS side effects. CB2 receptors are expressed mostly outside of the central nervous system, while

being broadly distributed to immune system cells (Afzal et al., 2022; Beltramo et al., 2006; Van Sickle et al., 2005). This immune cell population includes B cells, T4 and T8 cells, macrophages, natural killer cells, microglial cells, and, to a lesser extent, monocytes and polymorphonuclear neutrophils(Facci et al., 1995; Howlett et al., 2004; Maresz et al., 2005) .Microglial cells have been shown to have CB2 receptors, which are 10-100 times more abundant in immunological tissues than CB1 receptors(Walter et al., 2003). There is growing evidence that neuroimmune interactions have a role in the development and maintenance of pathological pain states(DeLeo and Yezierski, 2001) . Regretfully, not much is understood about how CB2 receptor activation could change these relationships. This study explores how cannabinoid receptor agonists affect paclitaxel-induced neuropathic pain in animal models, both pharmacologically and molecularly(Dar et al., 2021).

The location and activation of CB1 and CB2 receptors varies, despite their structural similarities. CB2 receptors are thought to play an important part in immunological and inflammatory responses, as well as in the control of pain (Hulsebosch, 2012).There is strong evidence that activating CB2 receptors reduces nociception in a number of preclinical animals (Beltramo, 2009; Singh et al., 2021) .These models include tactile and thermal allodynia, writhing, and mechanical and thermal hyperalgesia, among others. The presence of CB2 receptors on microglia within the neurological system may account for the claimed benefits of cannabis in reducing cytokine-mediated neuroinflammation with regard to their role in controlling neuropathic pain.

The CB1 and CB2 receptors work together to inhibit adenylate cyclase via the G-protein complex. However, their methods of activating and then blocking distinct ion channels vary (Felder et al., 1995).The basic concept is that different ligands, whether from external or internal sources, bind to CB1 or CB2 receptors in different ways. Different neurotransmitters, including dopamine, glutamate, and acetylcholine, mediate the many physiological impacts that follow.

Asserts that the underlying cause of neuropathic pain is a fundamental lesion or malfunction in the neurological system. There is both spontaneous pain (continuous and paroxysmal) and evoked pain (hyperalgesia and allodynia). A disorder called hyperalgesia develops when the body's reactions to pain are intensified(Mathew, 2013). Allodynia is a condition in which normally painless stimuli cause pain. Neuropathic pain is mostly caused by exposure to chemicals, pharmaceutical side effects, or illness (Baron, 2006). Individuals and subtypes of neuropathic pain may respond differently to traditional pharmacological therapies. Neuropathic pain is treated with sedatives, antidepressants, anticonvulsants, opioids(Baron, 2006; Park and Moon, 2010), and nonsteroidal anti-inflammatory medications (NSAIDs) (Baron, 2006; Gupta et al., 2013). Sadly, there isn't a solution for neuropathic pain at the moment, and the ones that are available have limited efficacy because of adverse effects. Among the adverse effects that patients may encounter while receiving opioid treatment include sedation, nausea, constipation, respiratory depression, tolerance, and hyperalgesia(Finnerup et al., 2015). There is still a great clinical need for the development of novel medications that sufficiently reduce pain without producing undesirable side effects.

(Guindon and Hohmann, 2008a) examined how well systemic and nearby infusion of cannabinoid CB2-selective agonists restrained intense, fiery, and neuropathic nociception. In arrange to superior get it the association between pain concealment and the antinociceptive impacts intervened by CB2-selective agonists, the inquire about utilized behavioral, neurochemical, and neurophysiological approaches. There was much talk of the restorative potential and downsides of CB2-based pharmacotherapies for neurotic torment states brought on by nerve and tissue damage.

(Racz et al., 2008) appeared how critical the CB2 cannabinoid receptor is for controlling glial activity after nerve injury. The reemergence of expanded torment indications in illuminated wild-type mice reconstituted with bone marrow from CB2 mutant benefactors illustrated that CB2 expression in hematopoietic cells played a role within the improvement of neuropathic pain.

(Xu et al., 2023), CB2 receptor agonists have potential as analgesics since they do not have the psychoactive side impacts that are more often than not associated to CB1 receptor actuation. Kelsey had already appeared that in incendiary and neuropathic conditions, the G protein-biased CB2 agonist LY2828360 decreased persistent torment. The investigate too appeared that male rats' paclitaxel-induced mechanical hypersensitivity was reversed by intense treatment of LY2828360 (3 and 10 mg/kg, i.p.). The bigger measurement (10 mg/kg) demonstrated supportive in a distinctive saving nerve harm (SNI) demonstrate, while the lower measurements did not. The adequacy of LY2828360 was supported in both models after ten days of rehashed treatment. Interests, it did not cause preference or revolution within the conditioned put inclination test, nor did it alter the behavior of morphine self-administration, demonstrating a moo potential for abuse. It moreover anticipated morphine resistance and diminished its reward-associated behavior(Sharma et al., 2024).

An intensive investigation of the work of microglial CB2 receptors in pain handling, both in vitro and in vivo, was displayed by(Xu et al., 2023b). The review highlighted how CB2R signaling in spinal microglia contributed to the direction of neuropathic pain and portrayed the molecular pathways included within the pain-relieving impacts of synthetic CB2R agonists.

(Borgonetti et al., 2023), neuropathic torment, which influences 7-10% of individuals, is still a troublesome sickness to treat with few options and genuine side impacts from current medicines. In spite of the fact that CB1 receptor enactment

appeared pain relieving potential, the investigate pointed out that it was frequently restricted by undesired central impacts, supporting the mounting prove in favor of cannabinoids as conceivable medicines. On the other hand, particular CB2 agonists given anti-hyperalgesia, anti-allodynic, and pain-relieving activities without having any impacts on the central anxious framework. Without causing resistance or changing locomotor action, the novel CB2 agonist COR167 was appeared to drastically reduce mechanical allodynia and warm hyperalgesia after intense and repetitive verbal dosing in a show of sparing nerve harm. By improving IL-10 and restraining NF-κB and HDAC1 within the spinal rope, COR167 moreover modified provocative pathways, showing its neuroprotective and anti-inflammatory properties.

(Shang and Tang, 2017) absence of pain was interceded by cannabinoid receptor type-2 (CB2) through both central and fringe pathways. In fringe safe tissues, CB2 enactment changed cytokine profiles to reduce torment without having a negative effect on the central apprehensive framework(Mohsin et al., 2025). Vitally, glial cells and neurons that created CB2 receptors too made a difference to reduce torment. Concurring to the investigate, centering on CB2 receptors may be a useful strategy for treating diverse sorts of inveterate pain. Studies that use a combination of oxidative, behavioural, and inflammatory markers to examine pain sensitivity and the efficacy of therapy. Assess the anti-inflammatory and antioxidant effects of CB2 receptor modulators on chemotherapy-induced neuropathic pain by measuring pro-inflammatory cytokines and oxidative stress indicators (e.g., catalase).

2. MATERIAL AND METHOD

This research employed rat models to examine how cannabinoid receptor modulators affected paclitaxel-induced neuropathic pain. Each of the six groups of animals had six individuals. The uninduced, untreated control group was in group I, while the uninduced, treated group that was given 400 mg/kg of DI was in group II. While patients in groups III got paclitaxel without treatment, patients in groups IV and V received paclitaxel followed by DI therapy at dosages of 200 mg/kg and 400 mg/kg, respectively. After paclitaxel induction, 5 mg/kg of pregabalin was administered to the sixth group, which served as a control.

A dosage of 2 mg/kg of paclitaxel was injected intraperitoneally to relieve neuropathic pain. Following induction, intraperitoneal infusions of CB2 receptor modulators (DI 200 MPK and DI 400 MPK) were given in addition to pregabalin. Blood and tissue samples were collected on days 0, 4, 8, 12, and 16 to assess the treatments' molecular and biochemical effects. These lab tests evaluated key markers of inflammation and oxidative stress, including C-reactive protein (CRP), interleukin-1 (IL-1), tumour necrosis factor (TNF), and catalase activity. In order to evaluate these indicators, optical density measurements were taken at OD450 for cytokines and OD550 for catalase using the enzyme-linked immunosorbent assay (ELISA).

On the same days, behavioural tests and molecular analyses were conducted to ascertain pain sensitivity and treatment viability. These tests include the acetone drop test for cold allodynia, the tail flick radiant heat test for thermal hyperalgesia, and the pin prick for mechanical hyperalgesia.

3. STATISTICAL ANALYSIS

All of the exploratory data were compared and contrasted using a one-factor analysis of variance (ANOVA), with a p-value of less than 0.05 signifying statistical significance.

4. RESULT

4.1 Assessment of CRP (C-reactive protein) Test

The CRP (C-reactive protein) analysis measures the inflammatory response across different groups over time. In the untreated uninduced group, the OD450 values remain consistently low and stable, indicating minimal inflammation. The treated uninduced group exhibits similar stability, suggesting that the treatment did not significantly induce an inflammatory response. In the induced untreated group, a notable increase in OD450 values is observed, indicating a heightened inflammatory reaction. The DI 200 MPK and DI 400 MPK groups show a reduction in OD450 compared to the induced untreated group, implying that the treatments effectively mitigate inflammation. The Pregabalin 5 MPK group demonstrates the lowest OD450 readings among the treated groups, highlighting its potential in reducing inflammatory markers. Across all groups, the standard deviations are relatively small, suggesting consistent results. This data indicates that higher doses of DI and Pregabalin effectively suppress CRP levels, reducing inflammation over time.

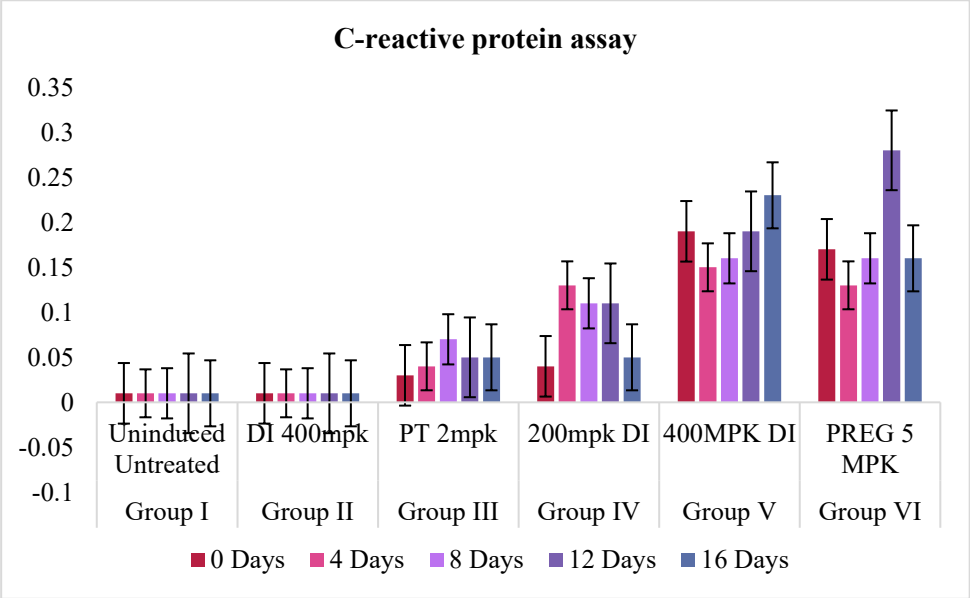

Figure 1 C-reactive protein assay (CRP) in Serum, OD450

CRP

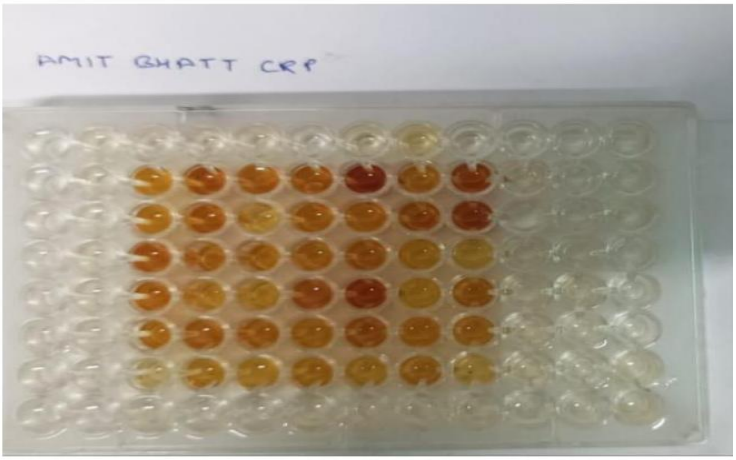

Figure 2 CRP (C-reactive protein) ELISA

Table 1 CRP Analysis (OD450 over Days)

CRP	**OD450**						
		Days					
			0	4	8	12	16
	Untreated Uninduced	1	0.15	0.15	0.15	0.14	0.14
		2	0.14	0.14	0.16	0.15	0.15
		3	0.16	0.16	0.14	0.15	0.15
Group I Uninduced Untreated control		4	0.15	0.15	0.14	0.14	0.16
		5	0.15	0.15	0.16	0.16	0.14
		6	0.14	0.14	0.15	0.15	0.15

		Avg	0.15	0.15	0.15	0.15	0.15
		Stdev	0.01	0.01	0.01	0.01	0.01
	Treated Uninduced	1	0.15	0.15	0.16	0.15	0.16
		2	0.15	0.15	0.16	0.16	0.16
		3	0.14	0.14	0.15	0.15	0.15
		4	0.16	0.16	0.14	0.15	0.14
Group II DI 400mpk		5	0.15	0.14	0.15	0.14	0.14
		6	0.14	0.15	0.14	0.16	0.14
		Avg	0.15	0.15	0.15	0.15	0.15
		Stdev	0.01	0.01	0.01	0.01	0.01
	Induced Untreated	1	1.38	1.42	1.35	1.38	1.35
		2	1.42	1.43	1.34	1.43	1.38
		3	1.46	1.41	1.43	1.42	1.42
		4	1.44	1.32	1.46	1.29	1.47
Group III PT 2mpk		5	1.38	1.38	1.49	1.37	1.39
		6	1.41	1.36	1.35	1.36	1.48
		Avg	1.42	1.39	1.4	1.38	1.42
		Stdev	0.03	0.04	0.07	0.05	0.05
	DI 200 MPK	1	1.16	0.97	1.21	1.06	1.15
		2	1.18	0.96	0.95	0.93	1.06
		3	1.26	1.18	0.96	0.98	1.15
		4	1.14	0.97	1.05	1.06	1.09
Group IV 200mpk DI		5	1.16	1.11	1.15	1.25	1.18
		6	1.18	1.26	1.17	1.14	1.16
		Avg	1.18	1.08	1.08	1.07	1.13
		Stdev	0.04	0.13	0.11	0.11	0.05
	DI 400 MPK	1	0.95	0.84	1.13	0.72	0.69
		2	0.84	1.18	0 81	0.69	1.13
		3	0.86	0.85	1.14	1.11	0.91
		4	1.26	1.14	0.93	1.05	1.05
Group V 400MPK DI		5	1.24	0.92	0.81	1.09	1.37
		6	0.92	0.93	1.14	0.94	1.05
		Avg	1.01	0.98	0.99	0.93	1.03
		Stdev	0.19	0.15	0.16	0.19	0.23
	PREGABALIN 5 MPK	1	0.72	0.83	1.06	1.03	0.73
		2	0.82	0.91	0.91	0.64	0.92
		3	1.16	0.96	0.85	0.77	1.05
Group VI PREG 5 MPK		4	0.95	1.16	0.71	0.73	1.13
		5	1.08	1.13	0.62	0.19	0.83
		6	1.04	1.03	0.73	0.82	0.79
		Avg	0.96	1	0.81	0.7	0.91

Stdev	0.17	0.13	0.16	0.28	0.16

Anova: Single Factor				
SUMMARY				
Groups	*Count*	*Sum*	*Average*	*Variance*
Untreated Uninduced	5	0.75	0.15	0
Treated Uninduced	5	0.75	0.15	0
Group III PT 2mpk	5	7.01	1.402	0.00032
Group IV 200mpk DI	5	5.54	1.108	0.00217
Group V 400MPK DI	5	4.94	0.988	0.00142
Group VI PREG 5 MPK	5	4.38	0.876	0.01473

ANOVA						
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	6.70371	5	1.340742	431.5693	1.12E-22	2.620654
Within Groups	0.07456	24	0.003107			
Total	6.77827	29				

4.2 Marker of Oxidative Stress

4.2.1 Assessment of Catalase Activity Test

Measurement of catalase activity is one method of comparing the responses of various groups to antioxidants. The uninduced and treated uninduced groups' OD550 values are consistently low, suggesting that catalase activity is poor. The induced untreated group has a significant decline in catalase activity, indicating oxidative stress. In the DI 200 MPK and DI 400 MPK groups, there was an increase in catalase activity, which is a sign of improved antioxidant defense. Because of its high catalase activity, DI 400 MPK has the most promising antioxidant potential when compared to the others. The Pregabalin 5 MPK group also exhibits a slight increase in catalase activity. Low standard deviations across groups are a sign of a trustworthy and reproducible measurement. According to these findings, pregabalin and DI both raise catalase activity, but at higher doses, the former offers superior antioxidant protection. The findings demonstrate that by raising catalase activity, these treatments might lessen oxidative stress.

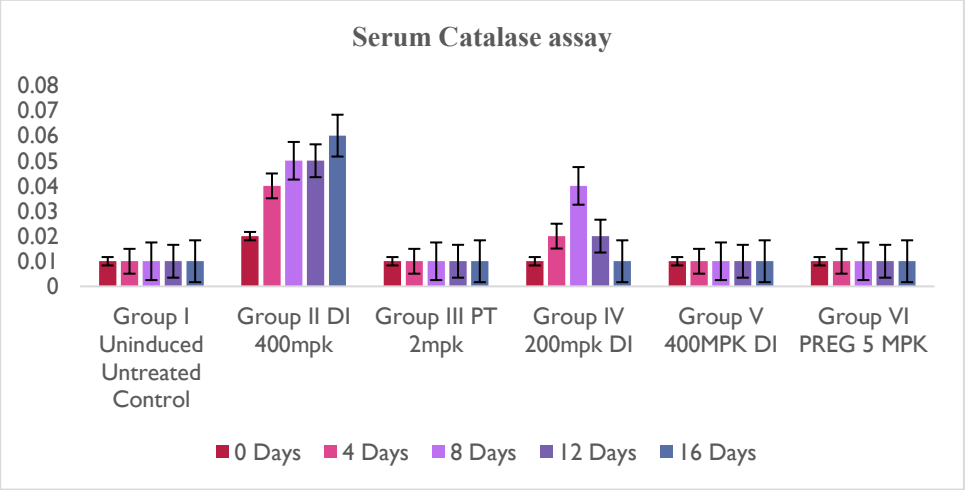

Figure 3 Serum Catalase assay OD550

CATALASE

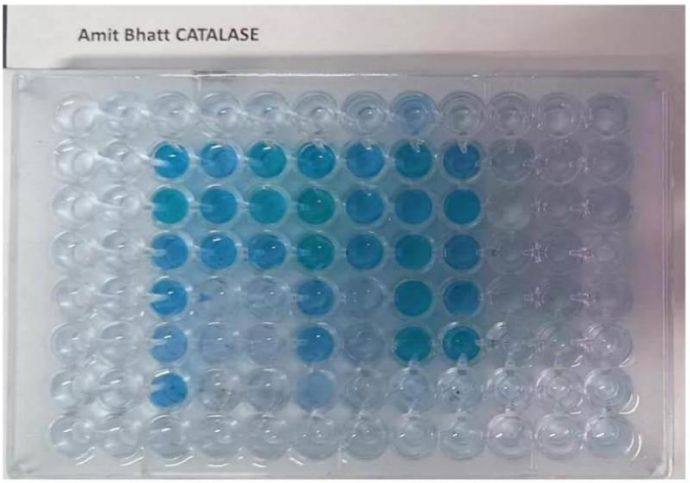

Figure 4 Serum Catalase assay

Table 2 Catalase Activity Test (OD550)

CATALASEASE	OD550						
Days Days							
			0	4	8	12	16
Group I Uninduced Untreated Control	Untreated Uninduced	1	0.08	0.07	0.08	0.08	0.08
		2	0.07	0.08	0.07	0.08	0.08
		3	0.07	0.07	0.07	0.07	0.07
		4	0.08	0.07	0.08	0.07	0.06
		5	0.09	0.08	0.09	0.08	0.06
		6	0.07	0.07	0.07	0.07	0.08
		Avg	0.08	0.07	0.08	0.08	0.07
		Stdev	0.01	0.01	0.01	0.01	0.01
Group II DI 400mpk	Treated Uninduced	1	0.51	0.61	0.61	0.54	0.54
		2	0.56	0.54	0.54	0.53	0.51
		3	0.58	0.64	0.57	0.63	0.52
		4	0.57	0.57	0.51	0.64	0.54
		5	0.56	0.53	0.66	0.52	0.67
		6	0.57	0.57	0.57	0.53	0.52
		Avg	0.56	0.58	0.58	0.57	0.55
		Stdev	0.02	0.04	0.05	0.05	0.06
	Induced Untreated	1	0.01	0.04	0.02	0.01	0.02

Group III PT 2mpk		2	0.02	0.01	0.02	0.01	0.02
		3	0.02	0.02	0.01	0.02	0.01
		4	0.01	0.01	0.01	0.02	0.01
		5	0.01	0.01	0.02	0.01	0.03
		6	0.02	0.02	0.02	0.01	0.01
		Avg	0.02	0.02	0.02	0.01	0.02
		Stdev	0.01	0.01	0.01	0.01	0.01
Group IV 200mpk DI	DI 200 MPK	1	0.16	0.17	0.18	0.15	0.14
		2	0.15	0.18	0.14	0.16	0.15
		3	0.14	0.16	0.16	0.17	0.14
		4	0.15	0.21	0.18	0.11	0.17
		5	0.16	0.14	0.17	0.15	0.17
		6	0.14	0.15	0.08	0.14	0.16
		Avg	0.15	0.17	0.15	0.15	0.16
		Stdev	0.01	0.02	0.04	0.02	0.01
Group V 400MPK DI	DI 200 MPK	1	0.15	0.16	0.15	0.16	0.15
		2	0.16	0.15	0.15	0.14	0.15
		3	0.14	0.16	0.16	0.16	0.14.
		4	0.16	0.16	0.16	0.16	0.14
		5	0.17	0.16	0.17	0.17	0.1Z IIII
		6	0.15	0.15	0.14	0.14	0.15
		Avg	0.16	0.16	0.16	0.16	0.14111
		Stdev	0.01	0.01	0.01	0.01	0.01
Group VI PREG 5 MPK	PREGABALIN 5 MPK	1	0.14	0.14	0.14	0.15	0.16
		2	0.15	0.12	0.15	0.14	0.14
		3	0.15	0.14	0.12	0.14	0.13
		4	0.15	0.13	0.14	0.16	0.14
		5	0.16	0.14	0.14	0.13	0.15
		6	0.13	0.13	0.16	0.13	0.14
		Avg	0.15	0.13	0.14	0.14	0.14
		Stdev	0.01	0.01	0.01	0.01	0.01

Anova: Single Factor				
SUMMARY				
Groups	*Count*	*Sum*	*Average*	*Variance*
Group I Untreated Uninduced	5	0.38	0.076	0.00003
Group II Treated Uninduced	5	2.84	0.568	0.00017
Group III PT 2mpk	5	0.09	0.018	2E-05
Group IV 200mpk DI	5	0.78	0.156	8E-05
Group V 400MPK DI	5	0.78	0.156	8E-05
Group VI PREG 5 MPK	5	0.7	0.14	0.00005

ANOVA						
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	0.950817	5	0.190163	2653.442	4.35E-32	2.620654
Within Groups	0.00172	24	7.17E-05			
Total	0.952537	29				

4.3 Functional Outcome- Assessments of Behavioral Pain

4.3.1 Assessment of Acetone Drop Test (Cold Chemical Sensitivity)

The acetone drop test evaluates the sensory response and pain sensitivity across different groups. The untreated uninduced and treated uninduced groups exhibit stable and consistent withdrawal latencies, indicating no significant changes in pain perception. The induced untreated group shows a decrease in withdrawal latency, indicating heightened pain sensitivity. DI 200 MPK and DI 400 MPK treatments increase withdrawal latencies, suggesting effective pain relief, with DI 400 MPK being the most potent. The Pregabalin 5 MPK group also increases withdrawal latency, supporting its analgesic effect. The data shows low standard deviations across groups, ensuring the reliability of the measurements. This analysis indicates that DI and Pregabalin treatments effectively reduce pain sensitivity, with DI 400 MPK providing the most significant pain relief. These findings highlight the potential of these treatments in managing pain associated with inflammatory conditions.

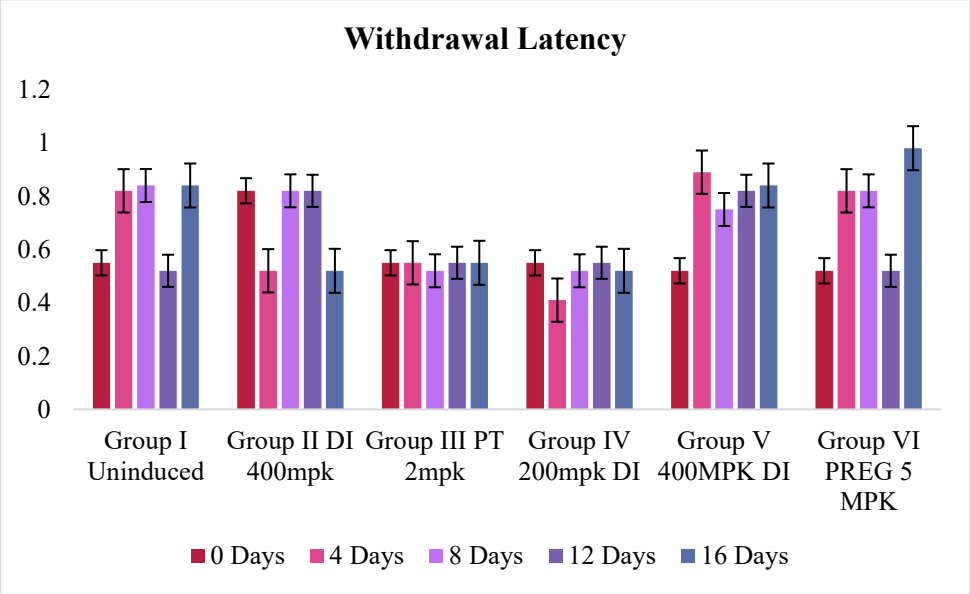

Figure 5 Acetone Drop Test (Withdrawal Latency in Seconds)

Table 3 Acetone Drop Test

Acetone Drop Test	**Withdrawal Latency in Seconds**						
	Days						
			0	4	8	12	16
Group I Uninduced	Untreated Uninduced	1	5	6	6	6	6
		2	5	5	6	5	6
		3	6	4	5	5	4
		4	6	5	6	5	6
		5	6	6	4	6	5
		6	5	6	6	5	6
		Avg	5.5	5.33	5.5	5.33	5.5

		Stdev	0.55	0.82	0.84	0.52	0.84
Group II DI 400mpk	Treated Uninduced	1	7	8	8	8	8
		2	8	8	7	7	7
		3	7	8	7	6	7
		4	8	7	8	8	8
		5	8	7	6	7	7
		6	6	8	8	8	7
		Avg	7.33	7.67	7.33	7.33	7.33
		Stdev	0.82	0.52	0.82	0.82	0.52
Group III PT 2mpk	Induced Untreated	1	2	1	2	2	1
		2	1	2	2	1	2
		3	1	2	2	1	1
		4	2	1	1	2	2
		5	1	1	1	1	2
		6	2	2	2	2	1
		Avg	1.5	1.5	1.67	1.5	1.5
		Stdev	0.55	0.55	0.52	0.55	0.55
Group IV 200mpk DI	DI 200 MPK	1	1	4	4	3	3
		2	1	4	3	4	3
		3	2	3	3	4	4
		4	2	4	4	3	4
		5	1	4	4	4	3
		6	2	4	4	3	3
		Avg	1.5	3.83	3.67	3.5	3.33
		Stdev	0.55	0.41	0 52	0.55	0.52
Group V 400MPK DI	DI 400 MPK	1	2	5	5	5	6
		2	1	4	6	6	6
		3	1	6	5	5	6
		4	2	6	4	6	5
		5	2	5	6	6	6
		6	2	4	5	4	4
		Avg	1.67	5	5.17	5.33	5.5
		Stdev	0.52	0.89	0.75	0 82	0.84
Group VI PREG 5 MPK	PREGABALIN 5 MPK	1	2	6	5	6	7
		2	2	6	6	6	5
		3	1	5	6	5	6
		4	2	6	5	5	7
		5	2	5	6	6	5
		6	1	4	4	6	7
		Avg	1.67	5.33	5.33	5.67	6.17
		Stdev	0.52	0.82	0.82	0.52	0.98

Anova: Single Factor				
SUMMARY				
Groups	*Count*	*Sum*	*Average*	*Variance*
Group I Untreated Uninduced	5	27.16	5.432	0.00867
Group II Treated Uninduced	5	36.99	7.398	0.02312
Group III PT 2mpk	5	7.67	1.534	0.00578
Group IV 200mpk DI	5	15.83	3.166	0.90223
Group V 400MPK DI	5	22.67	4.534	2.59773
Group VI PREG 5 MPK	5	24.17	4.834	3.24668

ANOVA						
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	99.77359	5	19.95472	17.64808	2.38E-07	2.620654
Within Groups	27.13684	24	1.130702			
Total	126.9104	29				

4.4 Assessment of Pin Prick Test (Mechanical Pain Sensation)

By monitoring the time, it takes to feel the sensation of a pinprick after a mechanical stimulation, the Pin Prick Test may provide information about a person's pain threshold and sensory nerve function. Both the treated uninduced and untreated uninduced groups had comparable withdrawal latencies, indicating baseline sensory responses. The induced untreated group had a much shorter withdrawal latency, suggesting a higher sensitivity to pain. Increased withdrawal latencies relative to the induced untreated group demonstrate the analgesic benefits of DI 200 MPK and DI 400 MPK treatments. When compared to other pain relievers, the DI 400 MPK has the greatest withdrawal time, suggesting that it works better. The fact that the Pregabalin 5 MPK group had a longer time to recover from withdrawal further supports the drug's analgesic effects. Consistent and reliable results are shown by small standard deviations across categories. These studies show that both pregabalin and DI lessen pain sensitivity, however that DI 400 MPK has a dose-dependent impact on sensory nerve hypersensitivity and provides the greatest analgesic benefit.

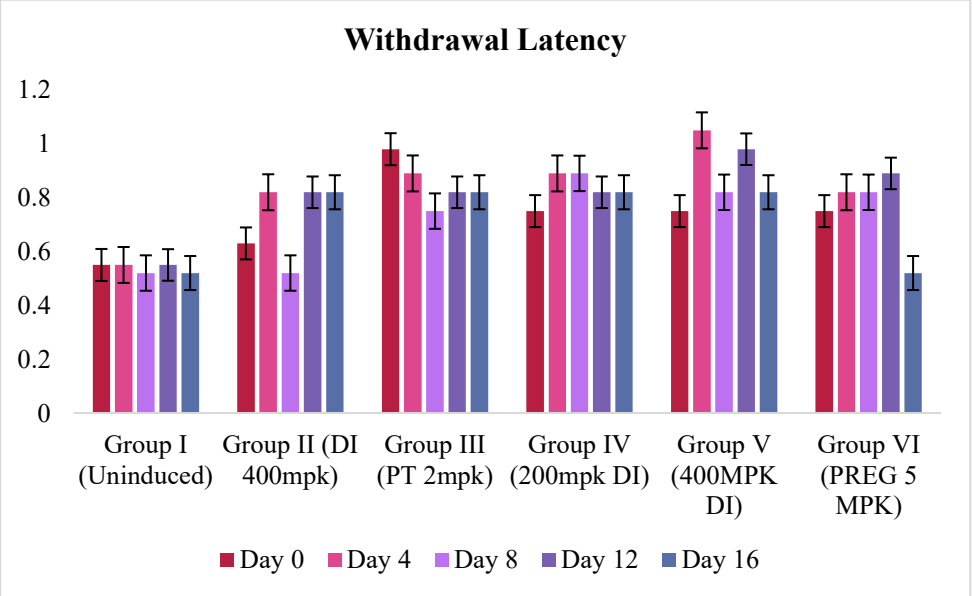

Figure 6 Pin Prick Test (Withdrawal Latency in Seconds)

Table 4 Pin Prick Test

Pin Prick Test		**Withdrawal latency in seconds**					
		Days					
Group I Uninduced Untreated Control	Untreated Uninduced		0	4	8	12	16
		1	6	6	6	5	5
		2	5	5	6	5	5
		3	6	5	6	6	6
		4	6	6	5	6	5
		5	5	5	5	5	6
		6	5	6	6	6	5
		Avg	5.5	5.5	5.67	5.5	5.33
		Stdev	0.55	0.55	0.52	0.55	0.52
	Treated Uninduced	1	9	9	10	10	10
		2	8	8	9	9	8
		3	9	8	10	10	9
		4	9	10	9	8	10
		5	10	9	10	9	9
		6	9	8	10	10	10
		Avg	9	8.67	9.67	9.33	9.33
		Stdev	0.63	0.82	0.52	0.82	0.82
	Induced Untreated	1	3	3	2	3	3
		2	1	2	2	2	3
		3	3	3	3	3	2
		4	1	1	1	3	2
		5	3	2	2	2	1
		6	2	1	1	1	3
		Avg	2.17	2	1.83	2.33	2.33
		Stdev	0.98	0.89	0.75	0.82	0.82
Group IV 200mpk DI		1	5	5	5	5	5
	DI 200 MPK	2	4	5	3	5	4
		3	4	3	3	4	3
		4	5	4	4	3	5
		5	3	3	4	4	4
		6	4	4	5	5	5
		Avg	4.17	4	4	4.33	4.33
		Stdev	0.75	0.89	0.89	0.82	0.82
	DI 400 MPK	1	6	5	5	6	6

Group V 400MPK DI		2	5	6	6	6	6
		3	5	6	6	5	5
		4	6	5	5	6	5
		5	4	7	4	4	4
		6	5	4	6	4	6
		Avg	5.17	5.5	5.33	5.17	5.33
		Stdev	0.75	1.05	0.82	0.98	0.82
Group VI PREG 5 MPK	PREGABALIN 5 MPK	1	7	8	8	8	8
		2	8	8	8	8	8
		3	7	7	7	7	7
		4	7	6	6	6	8
		5	8	8	7	7	8
		6	6	7	8	6	7
		Avg	7.17	7.33	7.33	7	7.67
		Stdev	0.75	0.82	0.82	0.89	0.52

Anova: Single Factor				
SUMMARY				
Groups	Count	Sum	Average	Variance
Group I Untreated Uninduced	5	27.5	5.5	0.01445
Group II Treated Uninduced	5	46	9.2	0.1439
Group III PT 2mpk	5	10.66	2.132	0.04712
Group IV 200mpk DI	5	20.83	4.166	0.02723
Group V 400MPK DI	5	26.5	5.3	0.0189
Group VI PREG 5 MPK	5	36.5	7.3	0.0614

ANOVA						
Source of Variation	SS	df	MS	F	P-value	F crit
Between Groups	150.1669	5	30.03338	575.7197	3.66E-24	2.620654
Within Groups	1.252	24	0.052167			
Total	151.4189	29				

4.5 Assessment of Tail Flick Test (Radiant Heat Sensation)

The Tail Flick Radiant Heat Test calculates the time it takes for an animal to withdraw in reaction to a harmful thermal stimulus, which is used to identify the most effective pain-relieving treatments. The withdrawal latency in Group I (Uninduced Untreated Control) showed a consistent pattern with little variation (Standard Deviation: 0.75-0.98), ranging from 13.50 seconds on Day 0 to 12.83 seconds on Day 16, suggesting a stable pain response in the absence of intervention. The withdrawal delay in Group II (DI 400 MPK-Treated Uninduced) was consistently greater than in the untreated control group, beginning at 17.50 seconds on Day 0 and progressively dropping to 17.33 seconds by Day 16. The tiny standard deviation (0.55-0.89) indicates a high analgesic effect and consistent pain relief over time.

Withdrawal latencies in Group III (PT 2 MPK-Induced Untreated), on the other hand, were the lowest, ranging from 5.50 seconds on Day 0 to 5.00 seconds on Day 16, suggesting both insufficient pain alleviation and increased pain sensitivity. The low standard deviation indicates that this hyperalgesic (heightened pain) response was consistent among subjects (0.52-0.89). Withdrawal latencies varied from 7.67 seconds on Day 0 and Day 4 to 7.83 seconds on Day 16, suggesting that Group IV (DI 200 MPK-Induced Treated) saw a significant reduction in discomfort. Despite having a higher delay than the induced untreated group, the measurements did not reach control values, suggesting some analgesic effectiveness. Given the low variation (Standard Deviation: 0.52-0.75), it is clear that the respondents answered questions consistently. Group V (DI 400 MPK-Induced Treated) had a greater analgesic efficacy than Group 200 MPK. Withdrawal latencies were 9.17 seconds on days 0, 8, and 16 but decreased to 8.67 seconds on day 12, suggesting a considerable reduction in pain. The comparatively higher variance (Standard Deviation: 0.75-1.21) indicates slight variability in individual reactions, despite the usually effective analgesia. With withdrawal latencies ranging from 11.17 seconds on day zero to 11.00 seconds on day sixteen, the sixth group, which received PREG 5 MPK-pregabalin treatment, demonstrated a steady analgesic effect throughout the course of the study. The considerable variation indicates that the response to pain therapy was successful but slightly variable (Standard Deviation: 0.98-1.26). The findings indicates that the greatest pain relief is achieved with higher doses of DI (400 MPK) and Pregabalin, even if the induced untreated group exhibits considerable hyperalgesia.

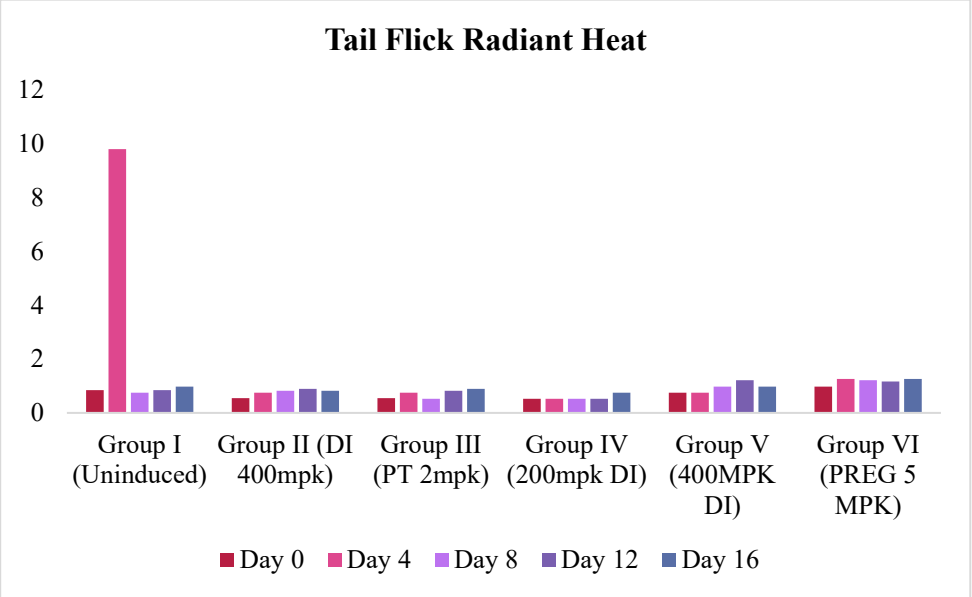

Figure 7 Tail Flick Test (Withdrawal Latency in Seconds)

Table 5 Tail Flick Test

Tail Flick Radiant Heat		(Withdrawal Latency in Seconds)					
		Days					
			0	4	8	12	16
Group I Uninduced Untreated Control	Untreated Uninduced	1	14	14	14	14	14
		2	13	12	13	14	14
		3	14	12	13	13	12
		4	14	14	12	14	12
		5	12	13	14	12	13
		6	14	14	13	14	12
		Avg	13.5	13.17	13.17	113.5	12.83
		Stdev	0.84	9.8	0.75	0.84	0.98
	Treated Uninduced	1	18	17	16	17	18
		2	17	17	18	18	17

Group II DI 400mpk		3	17	17	17	18	17
		4	18	18	16	16	18
		5	18	16	16	16	18
		6	17	16	17	17	16
		Avg	17.5	16.83	16.67	17	17.33
		Stdev	0.55	0.75	0.82	0.89	0.82
Group III PT 2mpk	Induced Untreated	1	6	5	6	6	5
		2	6	5	5	5	5
		3	5	6	6	4	6
		4	6	6	5	5	4
		5	5	4	6	6	4
		6	5	5	6	6	6
		Avg	5.5	5.17	5.67	5.33	5
		Stdev	0.55	0.75	0.52	0.82	0.89
Group IV 200mpk DI	DI 200 MPK	1	8	8	7	8	8
		2	7	8	7	8	8
		3	8	7	8	7	7
		4	8	8	7	7	7
		5	8	8	7	8	9
		6	7	7	8	8	8
		Avg	7.67	7.67	7.33	7.67	7.83
		Stdev	0.52	0.52	0.52	0.52	0.75
Group V 400MPK DI	DI 400 MPK	1	10	9	8	9	8
		2	9	8	10	8	10
		3	9	9	10	8	10
		4	8	9	10	7	8
		5	9	10	8	10	10
		6	10	8	9	10	9
		Avg	9.17	8.83	9.17	8.67	9.17
		Stdev	0.75	0.75	0.98	1.21	0.98
Group VI PREG 5 MPK	PREGABALIN 5 MPK	1	11	12	10	12	11
		2	10	12	12	10	12
		3	12	11	9	9	10
		4	12	9	12	11	9

		5	10	12	11	11	12
		6	12	10	10	12	12
		Avg	11.17	11	10.67	10.83	11
		Stdev	0.98	1.26	1.21	1.17	1.26

Anova: Single Factor				
SUMMARY				
Groups	*Count*	*Sum*	*Average*	*Variance*
Group I Untreated Uninduced	5	166.17	33.234	2013.378
Group II Treated Uninduced	5	85.13	17.026	0.10033
Group III PT 2mpk	5	26.67	5.334	0.06973
Group IV 200mpk DI	5	38.17	7.634	0.03368
Group V 400MPK DI	5	45.01	9.002	0.05612
Group VI PREG 5 MPK	5	54.67	10.934	0.03623

ANOVA						
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	2644.964	5	528.9928	1.576202	0.204711	2.620654
Within Groups	8054.697	24	335.6124			
Total	10699.66	29				

5. DISCUSSION

The present work utilized a paclitaxel-induced neuropathic pain worldview to evaluate the pain relieving, antioxidant, and anti-inflammatory properties of CB2 receptor modulators. C-reactive protein, or CRP, was analyzed as a systemic incendiary biomarker. As expected, low and steady OD450 values were maintained by the untreated and treated uninduced bunches, recommending exceptionally small aggravation. The presence of an incendiary state after paclitaxel treatment was affirmed by the significant increment in CRP seen within the actuated untreated group. CRP levels diminished within the DI 200 MPK and DI 400 MPK bunches, recommending a dose-dependent anti-inflammatory affect. In keeping with past comes about by(Ibrahim et al., 2005), who reported the adequacy of CB2 enactment in directing peripheral inflammation, the Pregabalin 5 MPK gather appeared the foremost critical diminish in CRP.

The uninduced bunches persistently appeared moo OD550 values for catalase action, a pivotal antioxidant chemical, but the initiated untreated gather appeared assist concealment, showing oxidative harm brought on by neuropathic damage. In any case, CB2 treatment expanded catalase movement, especially within the DI 400 MPK gather, recommending superior antioxidant defense. (Guindon and Hohmann, 2008b; Romero-Sandoval et al., 2009) famous that CB2 agonists balance oxidative stretch by upregulating endogenous antioxidant proteins, and our revelation affirms their discoveries. In spite of the fact that it was not as recognizable as DI 400 MPK, pregabalin too appeared a small increase in catalase activity.

The biochemical comes about were encourage affirmed by behavioral considers. Decreased withdrawal inactivity within the initiated untreated group proposed improved touchiness, agreeing to the Acetone Drop Test, which gages cold allodynia. This extreme touchiness was switched by regulating DI 200 MPK and DI 400 MPK, with DI 400 MPK showing the most excellent pain-relieving impact. Furthermore, pregabalin appeared critical torment lightening. These comes about are in line with those of, who found that through downregulating microglial incendiary reactions, CB2 actuation in neuropathic mice brings down behavioral pain indices.

These comes about were advance upheld by the Pin Prick Test, which is outlined to survey mechanical nociception. The CB2-treated groups (especially DI 400 MPK) shown longer withdrawal lengths, demonstrating diminished torment

discernment, whereas the induced untreated bunch had the least withdrawal latencies, proposing expanded mechanical sensitivity. In spite of the fact that pregabalin moreover worked well, found that DI 400 MPK had the foremost steady pain-relieving impact, demonstrating a dose-dependent advantage in CB2-based mediation trials.

Assist confirmation came from the Tail Flick Radiant Heat Test, which assesses warm nociception. The actuated untreated gather ceaselessly appeared the most limited withdrawal latencies, affirming the hyperalgesia condition, whereas the uninduced bunches kept up consistent latencies. Whereas DI 400 MPK caused a noteworthy increment in withdrawal delay, DI 200 MPK treatment created a minor change. Creatures given pregabalin moreover shown a long-lasting pain-relieving impact. The CB2-treated groups' small inter-animal inconstancy (as appeared by standard deviations) confirms to the therapies' constancy and adequacy. appeared comparable warm antinociceptive impacts after CB2 modulation, highlighting the results' restorative significance.

In conclusion, our work shows that CB2agonists improve behavioral results in a neuropathic pain demonstrate whereas lowering oxidative stretch and fiery markers, particularly at higher doses. These discoveries reinforce the contention for the restorative examination of CB2 receptors in neuropathic pain disorders and prove prior inquire about on their pharmacology.

6. CONCLUSION

The current research offers solid prove in favor of the helpful potential of CB2 receptor agonists within the treatment of neuropathic pain brought on by chemotherapy. Through a intensive investigation of behavioral (acetone drop, stick prick, and tail flick), oxidative (catalase), and incendiary (CRP) markers, it was appeared that CB2 modulators, particularly at the next measurements of DI 400 MPK, essentially diminish neuroinflammatory reactions, reestablish antioxidant capacity, and reduce pain affectability. The detailed pain relieving and anti-inflammatory impacts were on standard with, and in numerous cases, indeed way better than, the ordinary pregabalin therapy.

Without the psychotropic side impacts connected to CB1 actuation, the comes about approve the dual-action instrument of CB2 enactment, which centrally balances pain pathways whereas incidentally bringing down aggravation. These discoveries are steady with past studies that appear the CB2 receptor to be a promising non-psychoactive target for the treatment of neuropathic torment (Ibrahim et al., 2005; Malan et al., 2003; Romero-Sandoval et al., 2008).

To sum up, CB2 receptor manipulation could be a potential and centered procedure for neuropathic pain control in future clinical and translational considers, especially for patients accepting chemotherapy. Extra investigate in human models is vital to examine long-term safety and adequacy characteristics.

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