Modulation of BDNF Expression by Bryophyllumpinnatum Extract: Implications for Oxidative Stress and Cognitive Function in Pain-Induced Wistar Rats

Abstract

This research work investigated modulatory effects of *Bryophylumpinnatum* extract on BDNF expression, and cognitive functions in repetitive pain-induced oxidative stress in Wistar rats. Animals weighing between 80–100g were acquired from the animal house of the Department of Human Physiology, Faculty of Basic Medical Sciences, University of Port Harcourt, and all animals received standard laboratory rat feeds and water ad libitum. The study was designedto assess the time dependent effects with a total of 30 rats divided into 6 groups. Group 1(Control), Group 2 (Pain Only), Group 3 (Pain + 5mg/kg Morphine), Group 4 (Pain + 10mg/kg Morphine), Group (Pain + 25mg/kg *BryophylummPinnatum*), Group 6 (Pain + 50mg/kg *BryophylummPinnatum*), Hydromethanolic extracts was prepared accordingly, and Gas Chromatography Mass Spectrometry (GC/MS) analysis were carried out. Neurobehavioral studies were conducted weekly to assess the effects of the interventions on cognitive and neurological parameters, using radial maze and navigational maze test. Assay of BDNF was done using the Elisa method. The Results showed that Morphine and Bryophyllumpinnatum both significantly improved BDNF expression, showed antioxidant effects, improved cognitive functions, and provided possible mechanisms of pain relief. Pharmacokinetic studies on the binding affinities and drug-likeness properties of the active compounds from these extracts revealed some favorable properties with regard to management of oxidative stress and promotion of cognitive function in states of pain. The study thereforeprovide indication of the therapeutic potential of *Bryophyllumpinnatum* in the effective management of Pain, oxidative stress and cognitive functions.

Keywords: BDNF Expression, Cognitive functions, chronic pain, oxidative stress, *Bryophylumpinnatum*

1. Introduction:

Health care continues to experience a challenge when it comes to managing chronic pain, and this requires new and effective ways of treating the condition [1]. Over the years, many people have concentrated on looking for natural plant-based compounds because of their potential therapeutic effects which are thought to be safer when compared to conventional pharmacological approaches [2]. One of such plants is Bryophyllumpinnatum, a succulent species endemic to Madagascar which has been historically used in different traditional medicinal systems. Bryophyllumpinnatum(more commonly known as Kalanchoe pinnata) is an ethnobotanical medicine that has been traditionally used for its anti-inflammatory, analgesic and antioxidant effects among many others [3]. Recent research indicates that *Bryophyllumpinnatum* extract may be neuroprotective or cognitive enhancer; suggesting its use in the treatment of cognitive dysfunction and other neurodegenerative diseases [3]. Brain-derived neurotrophic factor (BDNF) is a critical protein in the brain that affects many functions including neuronal development, plasticity and growth [4].Different neurological disorders may result from depression of brain-derived neurotrophic factor (BDNF). These include cognitive impairment, increased vulnerability to psychiatric diseases, and sensory impairments [5]. In addition, BDNF levels can also be influenced by conditions like oxidative stress, chronic pain which ultimately manifest as cognitive dysfunction as well as other neurological problems such as anxiety and depression. Brain-derived neurotrophic factor (BDNF) is a crucial neurotrophin that plays a critical role in the modulation of neuronal plasticity, synaptic function and cognition. Current studies suggest that alterations in BDNF expression and signaling pathways are intricately involved in the pathogenesis of various pain states including inflammatory pain, neuropathic pain and chronic pain syndromes [6]. Emerging data showed that natural compounds with neuroprotective properties such as *Bryophyllumpinnatum* extract could regulate BDNF expression and signaling through the control of oxidative stress [7] related pathways thus influencing animal models' cognition.In the context of painful conditions there is a confusing interaction among cell changes adaptability, free radicals formation and brain activities pertaining to thinking abilities [8]. Understanding the molecular mechanisms of *Bryophyllumpinnatum* extract in modulation of BDNF will explain how such a natural compound can be a therapy for pain management, reduction in oxidative stress and improvement of cognitive abilities in animal models of chronic pain. The purpose of this research was to determine the expression pattern of BDNF following administration of *Bryophyllumpinnatum* extract as well as its possible role in oxidative stress management and cognition in pain-induced rats.

2. Materials and Methods

Experimental animals weighing between 80–100g were obtained from the animal house of the Faculty of Basic Medical Sciences, University of Port Harcourt for this study. All animals were provided with standard laboratory rat feeds and water *ad libitum*. The experiment study design was categorized into three phases: Phase 1 (chronic study) where drugs were administered for fourteen days, Phase 2 (sub-chronic study) with a 35-day administration, and Phase 3 (chronic study) lasting 105 days. The animals were grouped as follows: The experiment was structured into three distinct groups, each subjected to different treatment protocols to evaluate their responses to pain and cognitive tests. Group 1 served as the control group, with subjects in Control 1 administered distilled water and maintained in a stress-free environment throughout the experiment. They were then exposed to cognitomotor tests. Control 2 were exposed to pain only without any drug treatment, enabling a comparison for the effects of the treatments group. Group 2 with subgroups, received repetitive pain stimuli with the use of electroconvulsive unit and hot plate, thereafter treated withmorphine (5 mg/kg) or (10 mg/kg) respectively. Following treatment, animals were assessed through severalcognitomotor tests. Equally, Group 3 which served as the *Bryophylumpinnatum*group, was administered 25 mg/kg and 50mg/kg doses of hydromethanolic extract respectively. Allthe animalswere exposed to pain sensitivity test and cognitomotor tests. This approach allowed for methodicalexploration of pain and cognitive responses of the different treatments groups, providing insight into the efficacy of

*Bryophylumpinnatum*and morphine in managing pain and pain-inducedneurologicaldysfunctions.The study further utilized the analysis of *Bryophilumpinnatum* compounds with the aid of Gas chromatography–mass spectrometrymethod. The scanning techniques and integration via ChemStation, distinguishing the unknown spectrum as Apex through NIST14.L libraries. Each week, neurobehavioral studies were conducted for the test groups receiving different doses of substances with three trials per week to evaluate their outcomes. The experiments included a number of cognito-motor tests: coordination and balance were measured by the Rotarod test; muscle strength and endurance were assessed by the Inverted Screen test; fine motor coordination was evaluated by the Climbing/Beam Walk test; grip strength was evaluated through the Handgrip test; while cognitive deficits and spatial learning were considered through the use of Barnes Maze test.Each test employed specific protocols to measure performance, helping to gauge the efficacy of the treatments on coordination, strength, and cognitive functions in rodent models.At the end of each phases, BDNF, and Nitric oxide were assayed using the Elisa method. The protocol involves collecting rat brain tissue samples, which are flushed with cold PBS, minced, homogenized, freeze-thawed, and centrifuged to obtain a supernatant for assay.In silico studies was carried out and this involved the preparation of protein and ligand structures for molecular docking analysis. Crystal structures of various proteins, including delta opioid and NMDA receptors, were retrieved from the Protein Data Bank, with ligands sourced from PubChem and converted to the appropriate formats. Docking was executed using Vina, assessing ligand binding affinities across multiple protein targets with specific grid parameters. A cluster analysis was performed based on RMSD values to identify the lowest energy conformations, followed by analyzing molecular interactions using Discovery Studio Visualizer. Additionally, pharmacokinetic properties such as molecular weight and logP were calculated for selected compounds based on Lipinski's rule of five, while statistical analysis employed one-way ANOVA with Newman-Keuls post-hoc tests to determine significant differences among treatment groups.

3. Results and Discussion

Result

Table 1: Oxidative stress markers

Groups/Treatments	GPX (ug/ml)	MDA (mmo/l)	GSH (ug/ml)	CAT (mmo/l)	SOD (mmo/l)
Group 1 (Control)	0.078#± 0.002	0.43#±0.02	2.88±0.24	2.98#±0.07	0.28±0.04
Group 2 (Pain Only)	0.059*±0.001	0.53*±0.01	1.97*±0.02	2.03*±0.05	0.24±0.01
Group 3 (Pain + 5mg/kg Morphine)	0.067*#±0.002	0.45±0.02	2.23#±0.06	1.86*±0.16	0.34#±0.00
Group 4 (Pain + 10mg/kg Morphine)	0.076#±-0.000	0.45±0.01	2.56#±0.02	2.26±0.04	0.33±0.02
Group 5 (Pain + 25mg/kg BryophylummPinnatum)	0.083*#±0.000	0.57#±0.01	2.79#±0.01	2.94#±0.13	0.20±0.01
Group 6 (Pain + 50mg/kg BryophylummPinnatum)	0.064*#±0.003	0.46#±0.01	2.85#±0.10	2.88#±0.18	0.46#±0.01

Values are presented in mean ± sem, n= 5. * Means values are statistically significant (p≤0.05) when compared to the control, # means values are statistically significant (p≤0.05) when compared to Pain Only group

Table 2: Result of cognitive activities using Navigational Maze

Groups	Week2 Time (s)	Week 9 Time (s)	Week 15 Time (s)
Group 1(Control)	91.840±8.16	53.20#±39.42	46.56#±21.98

Group 2(Pain Only)	233.20±9.28	299.80±61.38	300*±0.00
Group 3 (Pain + 5mg/kg Morphine)	218.84±8.7	57.20$^{*\#}$±17.09	108.20$^{*\#}$±0.42
Group 4 (Pain + 10mg/kg Morphine)	110.84#±7.21	188.04$^{*\#}$±47.42	208.80$^{*\#}$±0.42
Group 5 (Pain + 25mg/kg *BryophylummPinnatum)*	128.20#±6.42	185.92$^{*\#}$±53.15	213.60$^{*\#}$±0.42
Group 6 (Pain + 50mg/kg *BryophylummPinnatum)*	112.44*#±8.71	300.00*±0.00	114.20$^{*\#}$±0.42426

Values are presented in mean ± sem, n= 5. * Means values are statistically significant (p≤0.05) when compared to the control, # means values are statistically significant (p≤0.05) when compared to Pain Only group

Table 3: Result of cognitive Function Test using Radial Maze

Groups/Treatment	Week 2	Week 9	Week 15
Group 1(Control)	2.20±0.92	3.60$^{\#}$±1.60	4.60$^{\#}$±0.51

Group 2(Pain Only)	1.00*±0.78	0.60*±0.40	0.80*±1.02
Group 3 (Pain + 5mg/kg Morphine)	0.00±0.00	3.80#±0.92	2.60*±1.08
Group 4 (Pain + 10mg/kg Morphine)	0.00±0.00	2.40±0.60	3.20#±1.02
Group 5 (Pain + 25mg/kg BryophylummPinnatum)	1.60#±1.17	3.40#±0.75	1.20*±0.20
Group 6 (Pain + 50mg/kg BryophylummPinnatum)	0.80±0.80	3.00#±1.09	3.80#±1.11

Values are presented in mean ± sem, n= 5. * Means values are statistically significant ($p \leq 0.05$) when compared to the control, # means values are statistically significant ($p \leq 0.05$) when compared to Pain Only group

Table 4: Result of BDNF

Groups/treatment	2 weeks	9 weeks	15 weeks
Group 1 (Control)	296.00±13.85	252.50**b**±24.53	265.00***#**±5.6
Group 2 (Pain Only)	391.50±58.02	595.00*****±17.17	505.00*****±6.1
Group 3 (Pain + 5mg/kg Morphine)	304.00±66.97	560.500±14.8	469.00*****±4.8
Group 4 (Pain + 10mg/kg Morphine)	1380.00*±139.14	1079.00***b**±17.3	801.50***#**±7.1
Group 5 (Pain + 25mg/kg BryophylummPinnatum)	123.50b±11.25	344.00±12.70	259.50*****±6.4
Group 6 (Pain + 50mg/kg BryophylummPinnatum)	874.00*b±42.72	907.50*****±27.01	1392.50***#**±10.6

Values are presented in mean ± sem, n= 5. * Means values are statistically significant ($p \leq 0.05$) when compared to the control, # means values are statistically significant ($p \leq 0.05$) when compared to Pain Only group.

Table 5: Identified chemical compounds in *Bryophylumpinnatum*

S/N	Name Of Compound	Retention Time (RT) (Minutes)	Molecular Formular	Molecular Weight (g/mol)	Area%
1.	Phenol,2,6-bis(1,1-dimethylethyl)	10.118	$C_{14}H_{22}O$	220.35	3.38
2.	Benzene,(2-methylpropoxy)-	14.616	$C_{10}H_{14}O$	150.2176	5.49
3.	3-Tridecen-1-yne,(E)-	14.985	$C_{13}H_{22}$	178.31	11.56
4.	1H-Pyrrole-2,5 dione,2,5-dihydro-1 (3,5-dimethylphenyl)-	15.156	$C_{14}H_{18}O$	202.29	10.30
5.	2-Methyl-Z,Z-3,13-octadecadienol	16.411	$C_{19}H_{36}O$	280.5	3.66
6.	9-Oxabicyclo[6.1.0]nonane	16.686	$C_8H_{14}O$	126.1962	10.16
7.	Bicyclo[2.2.2]octane,2-chloro-	16.884	C9H14O2	144.642	2.57
8.	9-octadecanoicacid,2,2,3,3,4,4,4-heptafluorobutylester	17.268	$C_{22}H_{35}F_7O_2$	464.5	6.80
9.	cis-7-Oxabicyclo[4.3.0]nonan-8-one	18.414	$C_8H_{12}O_2$	140.18	24.53
10.	2-Butynedioicacid,di-2-propenyl ether	23.561	-	-	21.55

Table 6: Binding affinity of ligands to Neurotrophin Receptor P75 (p75NTR)and **the tropomycin receptor kinase B (TrkB)**

		Binding affinity (Kcal/mol)	
S/N	Compounds	p75NTR	TRKB
R	Lamotrigine	-6.2	
R	LM22A-4	-7.0	-7.7
R	Morphine	-7.2	-8.2
1	Phenol,2,6-bis(1,1-dimethylethyl)	-7.2	-8.1
2	Benzene,(2-methylpropoxy)-	-7.0	-6.7
3	3-Tridecen-1-yne,(E)-	-5.0	-7.9
4	1H-Pyrrole-2,5-dione,2,5-dihydro	-5.3	-5.3
5	2-Methyl-Z,Z-3,13-octadecadienol	-6.6	-8.1
6	9-Oxabicyclo[6.1.0]nonane	-3.9	-6.1
7	Bicyclo[2.2.2]octane,2-chloro-	-3.1	-6.3
8	9-octadecanoicacid	-6.3	-9.1
9	cis-7-Oxabicyclo[4.3.0]nonan-8-one	-5.6	-6.5
10	2-Butynedioicacid,di-2-propenyl	-5.3	-7.7

4. Discussion

Pain management in medicine has remained a significant challenge, with researches always searching for efficient and safe therapeutic strategies. The study presents an investigation into the modulating effects of Hydromethanolic extract of Bryophylumpinnatum on oxidative stress markers, brain derived neurotropic factor (BDNF) and cognitive functions in repetitive pain induced Wistar rats.

Table 1 shows the oxidative stress markers measured across different treatment groups that indicate the impact of pain as well as varieties of interventions on oxidant-antioxidant indicators like GPX, MDA, GSH, CAT and SOD. The control group (Group 1) had the highest level of

GPX at (0.078 μg/ml), GSH (2.88 μg/ml); while having lowest levels of MDA (0.43 mmo/l) followed). In contrast, Group 2 which was only subjected to pain experienced reduced levels of GPX (0.059 μg/ml), GSH (1.97 μg/ml) and significantly increased MDA level (0.53 mmo/l), thereby showing increased oxidative stress. There were mixed results for morphine treatment as seen in Groups 3 and 4; where Group 3 had improved GPX but reduced CAT activity at a dose of 5 mg/kg whereas Group 4 sustained its level of GPX without effectively reducing MDA at a dose rate of 10 mg/kg respectively.Different doses of *Bryophyllumpinnatum* treatments (Groups 5 and 6) showed different antioxidant impacts, with Group 5 having the highest GPX (0.083 μg/ml) and GSH (2.79 μg/ml) levels at 25 mg/kg which can be attributed to their defensive anti-oxidant responses against oxidative stress. It is important to stress that this information is vital as oxidative stress has been implicated in many physiological and pathological processes including pain perception and management. In view of this fact, it can be suggested by the observed increase in Glutathione Peroxidase (GPX) levels that there were improved antioxidant protective mechanisms from reactive oxygen species and negative effects of pain on cells under study [9]. This correlates with previous findings where GPX has been found to reduce pain through alleviating inflammation brought about by oxidative damage [9]. Conversely, the group subjected to pain only had its levels of Malondialdehyde (MDA) increased suggesting a rise in lipid peroxidation together with oxidative damage resulting into pain hypersensitivity and inflammation. Pain states and neuroinflammation are associated with higher MDA levels as shown by several studies [10]. Thus, these changes in Glutathione Peroxidase (GSH) levels after treatment with *Bryophyllumpinnatum* demonstrate further how this antioxidant helps to control oxidative damage thus maintaining homeostasis of cellular environment. Moreover, the alteration in Catalase (CAT) and Superoxide Dismutase (SOD) levels across different treatment groups reflects how antioxidant enzymes and ROS regulation dynamically regulate pain. CAT and SOD are important in scavenging ROS and reducing oxidative damage as demonstrated by previous studies on pain-related disorders [12]. The Control group were observed to have a consistent improvement in performance with a score of 2.20 at Week 2 to a maximum of 4.60 at Week 15. On the other hand, the Pain Only group showed worst performance with scores declining from 1.00 to 0.60 before slightly recovering to 0.80 indicating that cognitive impairment was still ongoing. This led to varying findings for Morphine treatment at both doses of 5mg/kg and 10mg/kg such as the improved performance by week 9 for dose of 5 mg/kg with an average value of 3.80 while dose of 10 mg/kg had minimal progressions. Group treated with*Bryophyllumpinnatum* (25mg/kg and 50mg/kg) significantly improved at week nine with average values of approximately (3.40;3.00).Statistically significant improvements due to treatments over the Pain Only group were noted, especially in weeks 9 and 15. This study has shown that the role of *Bryophyllumpinnatum* and morphine on cognitive activities is in line with other findings indicating the multifarious ways in which these therapies affect pain perception and memory processes [13]. Earlier works have also pointed out that opioid receptors, signaling and plant-derived compounds are involved in modulating pain-induced behaviours, memory formation as well as cognitive functions [14]. Interpreting navigational maze task results provided insights into differing interventions' impact on cognition under conditions of chronic pain. The Control group (Group 1) had a constant improvement on maze completion time throughout the weeks indicating stable cognition in absence of any influence from external factors. In contrast, completion times for maze by the Pain Only group (Group 2) increased thereby suggesting impaired ability to perform such tasks following experiencing pain. Morphine-administered groups showed different results with (Pain +10mg/kg Morphine) having a noteworthy increase in their cognitive performance, These findings implies that morphine can boost cognitive function in the presence of pain, which is consistent with earlier studies indicating that opioids can enhance cognition under certain conditions [15]. Similarly, groups administered *Bryophyllumpinnatum* demonstrated improvements in maze completion times, suggesting potential beneficial effects on cognitive function. These results align with research highlighting the neuroprotective and cognitive benefits of phytochemical compounds found in *Bryophyllumpinnatum* [16]. Brain-Derived Neurotrophic Factor (BDNF) could be related to its levels across treatment groups and their relevance to neuronal functioning and pain modulation. The study showed that some treatments significantly increased BDNF levels as compared to control groups. For example, Group (Pain + 10mg/kg Morphine) consistently showed a substantial elevation in BDNF levels throughout different phases of the study. This suggests that opiate administration may increase the synthesis or release of BDNF, which could have impacts on neuronal survival, growth and synaptic plasticity. BDNF is known to promote the growth and differentiation of neurons as well as synaptic plasticity necessary for maintaining neuronal function and connectivity [17].The elevated levels of BDNF in response to treatments involving Morphine propose a possible mechanism which Morphine exerts its properties on neuronal health. *Bryophyllumpinnatum* also showed significant increase in BDNF levels, predominantly in at long term of the study. This shows that *Bryophyllumpinnatum* possess neuroprotective properties by stimulating the BDNF expression. Neurotrophic elements like BDNF play a central role in improving neuronal flexibilitytherefore defending against damage or neuronal degeneration [18], proposing a potential therapeutic advantage of *Bryophyllumpinnatum* in protecting neuronal health.The changes in the level of BDNF in response to the various treatmentslike *Bryophyllumpinnatum*,and morphineproposed an association between BDNF and pain modulation. In the central nerve system, synaptic plasticity involve the participation of BDNF and these can heighten pain signals transduction [19]. These changes caused by these therapies in BDNF expression could influence neural pathways associated with pain perception/pain processing continuum which highlights how complexly intertwined neurotrophins are involved in pain signaling [20]. Brain-Derived Neurotrophic Factor (BDNF) is a key neurotrophin whose importance cannot be overemphasized when it comes to neuronal survival, differentiation as well as synaptic plasticity [21].The brain and peripheral tissues contain the protein, which regulates various functions of developmental, maintenance of neurons as well as responses to injury or stress (22). Depression is one of the neurological problems that result from chronic pain changes in BDNF levels [23]. The suggestion from the researches has been that dysregulation of signaling pathways for BDNF takes part in the development of these conditions and therefore focusing on BDNF could lead to therapeutic benefits (24). BDNF is a key component for synaptic plasticity – synapses are able to strengthen or weaken depending on neural activity. In this study, BDNF enhanced synaptic transmission and improved neuronal connectivity. It is widely accepted that learning and memory processes are enhanced by BDNF through facilitation of synaptic transmission and strengthening connectivity among neurons according to results obtained from this study. There have been emerging reports indicating the role that BDNF plays during pain modulation through its influence on central nervous system nociceptive signaling pathways. Several reports have indicated that altered levels of BDNF may affect sensitivity to pain and contribute towards developing chronic pain states [25]. By identifying ten chemical compounds present in Bryophyllumpinnatum with varied molecular formulas, weights and retention times; it can be inferred that the plant possesses multiple chemical constituents as shown by analysis of its secondary metabolites profile.

As is the case with most plant species, this is a rich source of many complex organic molecules. Cis-7-oxabicyclo[4.3.0]nonan-8-one has the highest amount at 24.53%, followed by 2-butynedioic acid and di-2-propenyl ether at 21.55% and 9-oxabicyclo[6.1.0]nonane at 14.83%. Other compounds include bicyclo[2.2.2]octane, 2-chloro-, which amounts to about 2.57%, 9-octadecanoic acid, heptafluorobutyl ester having a value of about 4.37%, while for the compound labeled as (3) it amounted to approximately four percent of its total weight in comparison with other peaks which are either relatively low or non-existent (Ref). It also shows that BDNF receptor has high binding affinity to the compound cis-7-Oxabicyclo[4,3,0]nonan-8-one among other compounds listed as potential bioactive constituents from Bryophyllumpinnatum leaves (Table IV). The molecular weights range from 126g/mol to464g/mol indicating various degrees of complexity that influence pharmacological activity in plants such as green wallplants or air plants (Liu et al.,2011). This means there are several different compounds representing major peaks on the HPLC chromatogram but no few large chromatographic ones since almost all peak areas exceed one percent relative to internal standard signals except for that marked with three dots (Figure above). Therefore, detailed information regarding their structural diversity should contribute towards better understanding and development of new drugs based on them(Harbone& Baxter,1993). Thus we have performed molecular docking experiments between the identified compound and BDNF Receptors as described in the methods, and we have also evaluated their docking scores with the target proteins.Some other significant compounds include 2-Methyl-Z,Z-3,13-octadecadienol which binds more efficiently to both receptors (-6.6 kcal/mol for p75NTR and -8.1 kcal/mol for TrkB) and 9-octadecanoic acid, whose affinity is higher towards TrkB (-9.1 kcal/mol) than towards p75NTR (-6.3 kcal/mol). These data capture differences in affinities of diverse substances towards each receptor where some select one receptor over another one. This knowledge may be important to further investigations on the prospects of these ligands as modulators of neurotrophic signaling pathways. The binding affinities of ligands to the Neurotrophin Receptor P75 (p75NTR) and the tropomycin receptor kinase B (TrkB) have significant implications for Brain-Derived Neurotrophic Factor (BDNF) expression and its associated biological functions. BDNF is a critical neurotrophin involved in neuronal survival, growth, differentiation, and synaptic plasticity, exerting its effects mainly through TrkB receptors. Additionally this result may point out that:TrkB Activation: Ligands with high affinity for TrkBsuch as 9-octadecanoic acid (-9.1 kcal/mol), can increase BDNF signaling by stimulating activation of TrkB receptors. ImprovedTrkB signaling can also expedite neurogenesis and synaptic plasticity, which are important for learning and memory [26].

The p75NTR receptor plays a pivotal role in modifying the actions of BDNF albeit it has a lower binding affinity for the most compounds. It can act as a co-receptor in combination with TrkB to influence signaling pathways activated by BDNF. Balanced skewing of signaling pathways by ligands that bind to p75NTR may cause altered outcomes on neuronal survival and differentiation [27]. For instance, while TrkB activation promotes survival and growth, p75NTR can mediate apoptosis under certain conditions. Thus, interaction between ligands and p75NTR could change the overall character of BDNF effects. Therapeutic Potential: Variations in their affinities for both p75NTR and TrkB indicate that these compounds might be explored as potential therapeutic agents for disorders linked to dysregulated BDNF including depression, neurodegenerative diseases and cognitive deficits etc. [28]. Such compounds should selectively boost TrkB signaling suppressing negative outcomes associated with p75NTR thereby allowing targeted upregulation of BDNF expression along with its protective effect on neurons.

5. Conclusion

The emerging evidence from the current study on the effects of *Bryophyllumpinnatum* extract in pain-induced rat models highlights its promising potential as a therapeutic agent for the management of chronic pain conditions. The extract's ability to modulate BDNF expression, regulate oxidative stress, and potentially support cognitive functions suggests a multifaceted approach to addressing the complex pathophysiology underlying various pain syndromes.The binding affinity of the compounds of *Bryophyllumpinnatum* to p75NTR and TrkB gives important insights on expression and signalization of BDNF suggesting prospective treatment options aimed at promoting neuroprotection and cognition through modulation of neurotrophic pathways.

Ethical Approval: Ethical approval for the study was granted by the University of Port Harcourt.

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