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Original Research Article

Anti-neurological dysfunction of stone breaker (phyllanthus niruri linn) leaf extract caused from cold restrain stress induction in female wistar rats

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Abstract

Introduction: Stone breaker (Phyllanthus niruri (Linn.)) is a medicinal plant with long history of folkloric therapeutic use in the treatment of pathological conditions such as neurological diseases (Parkinson's, Alzheimer, memory and learning disorder).
Aim and Objectives: This study was designed to investigate the ameliorative potentials of stone breaker (Phyllanthus niruri (Linn.)) Leaf Extract (PLE) on Cold Restrain Stress (CRS)-induced neurological dysfunction in rat's model.
Materials and Methods: 25 Albino rats were divided into 5 groups of 5 wistar albino rats each, CRS method of induction were carried out for 3h/day for 7days followed by oral administration of PLE with doses of 100 and 200mg/kg BWT and 0.05mg/kg BWT of prazocin for 28days. In vivo inflammatory, excitatory, neuro- functional and behavioral indices were evaluated with the following assays; inflammatory assays (myeloperoxidase, TNF-α, IL-1β, IL-6 and xanthine oxidase), excitatory assay (Na+/K+ ATPase) and neuro- functional assay (dopamine concentration and activities of acetylcholinesterase, tyrosine hydroxylase and NADH-Ubiquinone dehydrogenase (Complex I enzyme)). The behavioral indices (Y-maze task were determined on the rats to monitor the extent of cerebral alternation.
Result: Tthis revealed that phyllanthus leaf extract (PLE) significantly ($p<0.05$) ameliorated the damage induced by CRS in the brain of the wistar rats establishing the ameliorative potential of PLE (Linn.) in the administered groups (100mg/kg and 200mg/kg BWT), with the effect evident by an improved behavioral index. The treatment suppressed the effects of CRS by increasing the activity in excitatory (Na+/K+ ATPase), Neuro-functional concentration/activities (Dopamine concentration, Tyrosine hydroxylase, NADH-Ubiquinone dehydrogenase (Complex I enzyme)) and significantly decreased the activity of acetyl cholinesterase.
Conclusion: Therefore, this study was carried out to determine its therapeutic potentials of stone breaker in the management neurodegenerative dysfunction, and this has been proven by the extract by inhibition observed on the inflamed tissue and as well increased on the memory indices declined by the CRS in the cause of induction, and as such stone breaker leaves would be a therapeutic agent in the management of neurological disorder or neurodegenerative diseases.

Keywords: Stone breaker, Cold Restrain Stress, Medicinal plant, Neurological, Diseases

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1. Introduction

The significance of medicinal plants in promoting individual and community health cannot be over-stated. Our understanding of their therapeutic properties has been shaped by centuries of trial and error, careful observation, and even insights gained from watching animals in their natural habitats. The World Health Organization consultative group defined a medicinal *plant* as "any plant which in one or more of its organs, contains substances that can be used for therapeutic purposes or which are precursors for the synthesis of useful drugs".[1] Many medicinal plants have historically shown effectiveness against pathogens, and some have been traditionally used to treat malaria despite limited scientific understanding of their mechanisms. This suggests that medicinal plants could be a valuable source of new compounds for developing antimalarial treatments.[2,3]

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However, Medicinal plants can be found with a wide variety of secondary metabolites/compounds for example tannins, terpenoids, alkaloids, anthraquinones, glycosides, carotenoids, phenols, pyrrolidine alkaloids, rotenone,[4] and flavonoids[5] including chalcones which determine the therapeutic potencies of the plants[5] and have made them more prominent over synthetic or manufactured drugs, as they possess phytochemicals for maintaining good health conditions.

Phyllanthus niruri L. (Euphorbiaceae) is a prevalent tropical plant with recognized medicinal properties. In various parts of the world, including Brazil, Asia, Thailand, China, and Africa, this plant is traditionally used to treat a range of ailments, including inflammation, hepatitis, fever, malaria, and gonorrhea.[6] It is also used for malaria treatment in some endemic areas. For example, in Nigeria, an aqueous extract from the whole *P. niruri* plant is been used to reduce malaria symptoms. The biological and pharmacological functions reported for *P. niruri* include antiplasmodial, antioxidant, hepatoprotective, nephroprotective and anti-diabetic properties.[7] Moreso, immunomodulatory effects of *P. niruri* on both adaptive and innate arms of the immune response have been reported in *vitro* and *in vivo* studies. It stimulates and boosts the proliferation of lymphocytes and macrophages in experimental animals. It was reported to be immunosuppressive in several conditions, as evident in the inhibition of sRBC-induced cell-mediated immune response in which interferon-gamma is involved, reduction of leukocytes in *Mycoplasma gallisepticum*-infected chicken, inhibition of carrageen-induced oedema and neutrophil migration upon its induction by thioglycolate in *Mus musculus* Swiss male mice and regulation of serum levels of primary and secondary antibodies. *P. niruri* has been reported to contain various biologically active plant chemicals, including flavonoids, lignans, terpenoids, saponins, alkaloids, and tannins.[8] Catechin, quercetin, and astragalin are bioactive compounds which have been abundantly identified in *P. niruri.*

Stress, both psychologically and physically, is common in everyday life, it also response to series of non-specific adaptive response that are produced from the body when the body senses to the homeostatic balance is altered. The duration and intensity of the stress can be classify as acute and chronic stress. Acute stress has a positive effect on the body, while chronic stress indicates that the body has been "overdrive" for a long period of time, which causes serious complications and even promote tumor occurrences. Common stress are categorized as physical (different physical, chemical, and biological stimuli), psychological (conflict, frustration, hatred, fear, etc.), and social (professional competition, work burden, etc.).[8]

The progressive degeneration of neurons, often resulting in cell death, is known as neurodegeneration. This underlying process contributes to various debilitating diseases, including Parkinson's, Alzheimer's, and Huntington's, which can disrupt essential functions like movement, balance, communication, breathing, and cardiac function. Many of these diseases may be genetic, or as a result of aging, and oxidative stress but sometimes a medical condition such as alcoholism, tumour or stroke may be the underlying cause. Other causes may be environmental factor which include toxins, chemicals, and viruses. Neurodegenerative diseases are incurable, and together with cerebro-vascular disorders they constitute an ever increasing health, social, and economic burden for developed Westernized countries. Gradually, they are creeping into developing countries as well. It is estimated that by 2050, there will be at least one person in every family suffering from one form of neurodegenerative or cerebrovascular disorder or the other. Therefore, this work is designed to investigate on the therapeutic potentials of stone breaker (*phyllanthus niruri* linn.) leaf extract on cold restrain stress induced neurological dysfunction in female rats.

2. Materials and Methods

2.1. Sample collection and preparation

P. niruri leaf was collected at a garden within the Federal University of Technology, Akure staff quarters, Nigeria. Sample was identified at Center for Research and Development (CERAD), Federal University of Technology, Akure.

2.2. Extraction of phytochemicals

The leaves of the plant was air-dried, macerated using an industrial blender. Powdered sample was desolved in an aqueous solvent to obtain filtrate. The filtrate was concentrated using a rotary evaporator, then lyophilized using freeze dryer. The extract will be stored in a refrigerator at 4^{o}C until when needed.

2.3. Evaluation of neuroprotective potentials of P. niruri Leaf extract

Investigation into Effects of *P. niruri* Leaf against CRS-Induced learning and memory deficient.

Adult male Wistar rats, weighing 160-230 g were purchased from Experimental Animal Farm, Ogbomoso, Oyo State. Nigeria. All animals were maintained under controlled conditions of temperature (22±1°C), humidity (50-55%), and light (12 h light/12 h dark cycle). For 14 days before the start of the experiment, they were acclimatized to the laboratory conditions. Throughout the experiment, the animals have unlimited access to food and water.

The experiment was designed as follows with five (5) rats in each group:

Group 1: Sham-operated with oral administration of vehicle

Group 2: CRS–induce but not treated

Group 3: CRS–induced (3h/day), treated with 100mg/kg BWT of PLE
Group 4: CRS–induced (3h/day) treated with 200mg/kg BWT of PLE
Group 5: CRS–induced (3h/day) treated with prazosin 0.5mg/kg BWT i.p
Necropsy, Blood Collection and Preparation

Rats were sacrificed by cervical dislocation within eighteen hours from the last administration. The cardiac puncture was used to obtain blood samples, which were then placed in non-anticoagulant serum tubes and left to stand for 1h. The clotted blood was centrifuged at 3000rpm for 10min at 4^0C. The serum supernatant was pipetted into clean serum tubes before the evaluation of biochemical indices.

2.4. Preparation of tissue homogenates

The brain was rapidly cleaned in ice-cold 1.15% potassium chloride solution, then blotted and weighed. The tissues were subsequently homogenized in cold 0.1 M potassium phosphate buffer pH 7.4. The homogenates were cold-centrifuged for 10 min at 3000 rpm and supernatants were collected and stored at 4°C before biochemical assays.

2.5. Evaluation of neurofunctional indices

2.5.1. Determination of dopamine concentration

The concentration of dopamine was evaluated as described by Guo *et al.* (2009).

2.5.2. Evaluation of tyrosine hydroxylase activity

Tyrosine hydroxylase activity was measured by the slightly modified spectrophotometric method described by Shiman *et al.* (1971) and Crane *et al.* (1972)

2.6. NADH-Ubiquinone dehydrogenase (Complex I enzyme) Activity

Assay for NADH-Ubiquinone dehydrogenase (Complex I enzyme) activity was carried out using a modified method described by Saravanan *et al*. (2006),

2.6.1. Determination of acetylcholinesterase (AChE) activity

Activity of AChE was assessed by a modified spectrophotometric method as described by Ellman *et al.* (1961).

2.7. Evaluation of indices of apoptosis and inflammation

2.7.1. Determination of caspase-3 activity

Luciferase Substrate solution (Chemicon, 2002).

2.7.2. Determination of myeloperoxidase activity

Myeloperoxidase activity, an indicator of polymorphonuclear leukocyte accumulation, was determined according to the method of Eiserich *et al.* (1998).

2.7.3. Determination of xanthine oxidase activity

This was measured using the spectrophotometric method of Pradja and Weber (1975) as described by Mukaddes *et al.* (2006).

2.7.4. Determination of Tumor necrosis factor-α (TNF-α) Concentration

2.7.5. Determination of Interleukin-1 beta (IL-1β) Concentration

2.7.6. Determination of Interleukin-6 (IL-6) Concentration

3. Results

3.1. Apoptotic potentails of PLE

The effects of *Phyllanthus Niruri* extract on the activity of caspase were investigated in the management of neurological dysfunction in wistar rats as revealed in **Figure 1**. The results revealed that neurological dysfunction group (Group 2) caused reduced activity of caspase significantly compared to the treatment groups ($p \leq 0.05$). There was significant increase in caspase activity by both doses of *Phyllanthus Niruri* (Group 3, 4) ($p \leq 0.05$).reference group).

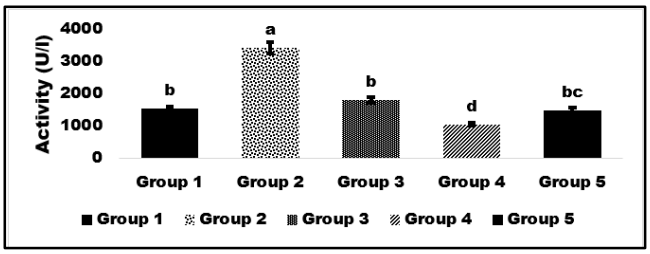

Figure 1: Effects of PLE on the activity of caspase-3 in neurological dysfunction wistar rats. Results were presented as mean±standard deviation where n=5. Values with different superscripts are significantly different ($p \leq 0.05$).

Treatments:
Group 1: Negative Control;
Group 2: CRS assault without treatment (Positive Control);

Group 3: CRS assault and 100mg/kg BWT of PLE extract;

Group 4: CRS assault and 200mg/kg BWT of PLE extract; and
Group 5: CRS assault with prazosin (0.5 mg/kg).

3.2. Anti-inflammatory potential of PLE

The effects of *P. niruri* extract on the activity of xanthine oxidase were investigated in the management of neurological dysfunction in wistar rats as revealed in **Figure 2**. The results revealed that neurological dysfunction induced not treated group (Group 2) caused increase in activity of xanthine oxidase significantly compared to the treatment groups ($p \leq 0.05$). There was significant decreased in xanthine

oxidase activity by both doses of *P. niruri* (Group 3 and 4) ($p \leq 0.05$).

Figure 3 Revealed the effects of *P. niruri* extract on the activity of myeloperoxidase in the management of neurological dysfunction in wistar rats. The results revealed that neurological dysfunction group (Group 2) caused increase in activity of myeloperoxidase significantly compared to the treatment groups ($p \leq 0.05$). There was significant decreased in myeloperoxidase activity by both doses of *P. niruri* (Group 3 and 4) ($p \leq 0.05$).

Figure 4 revealed the concentration of α-Tumor Necrosis Factor, it was shown that, there was a significant increase ($p<0.05$) in the concentration of α-Tumor Necrosis Factor in the brain of CRS-induced rats group (positive control group) compared to the experimental groups. Treatment with PLE significantly decreased the concentration of α-Tumor Necrosis Factor in a dose-dependent manner ($p<0.05$).

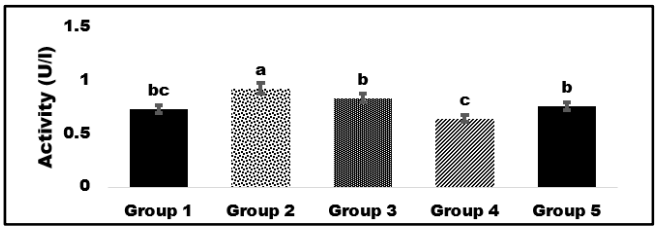

Figure 2: Effects of PLE on the xanthine oxidase activity of in neurological dysfunction wistar rats. Results were presented as mean±standard deviation where n=5. Values with different superscripts are significantly different ($p \leq 0.05$).

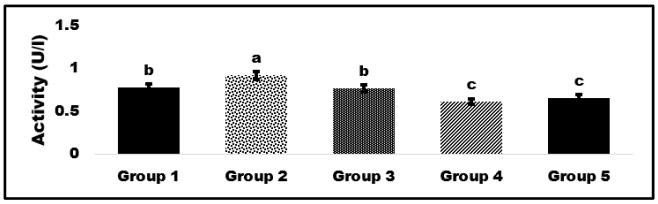

Figure 3: Effects of PLE on the myeloperoxidase activity of in neurological dysfunction wistar rats. Results were presented as mean±standard deviation where n=5. Values with different superscripts are significantly different ($p \leq 0.05$).

Figure 5 revealed the concentration of Interleukin-6, it was shown that, there was a significant increase ($p<0.05$) in the concentration of Interleukin-6 in the brain of CRS-induced rats group (positive control group) compared to the experimental groups. Treatment with PLE significantly decreased the concentration of Interleukin-6 in a dose-dependent manner ($p<0.05$).

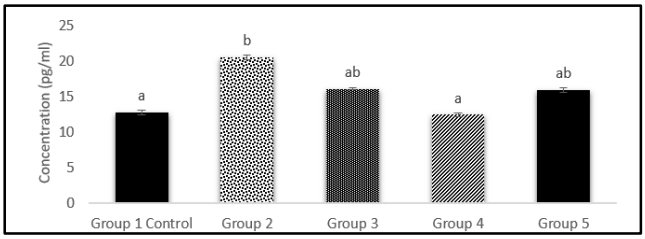

Figure 4: Effects of PLE on the activity of α-Tumor Necrosis Factor in neurological dysfunction wistar rats. Results were presented as mean±standard deviation where n=5. Values with different superscripts are significantly different ($p \leq 0.05$).

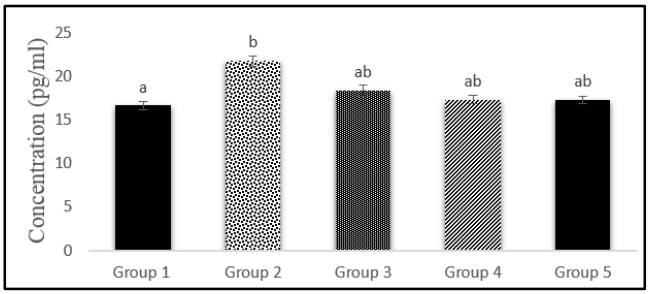

Figure 5: Effects of PLE on the activity of of Interleukin-6, in neurological dysfunction wistar rats. Results were presented as mean±standard deviation where n=5. Values with different superscripts are significantly different ($p \leq 0.05$).

3.3. Cyto-excitatory potential of PLE

The effects PLE on the activity of Na^+/K^+ ATPase were investigated in the management of neurological dysfunction in wistar rats as revealed in **Figure 6**. The results revealed that the neurotoxic group (Group 2) caused reduced activity of Na^+/K^+ ATPase significantly compared to the treatment groups ($p \leq 0.05$). There was significant increase in Na^+/K^+ ATPase activity by both doses of PLE (Group 3, 4) as well as the control group.

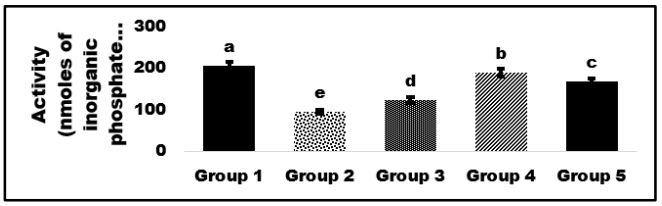

Figure 6: Effects of PLE on the Na^+/K^+ ATPase activity of in neurological dysfunction wistar rats. Results were presented as mean±standard deviation where n=5. Values with different superscripts are significantly different ($p \leq 0.05$).

3.4. Neuroprotective potential of PLE

Brain dopamine level (**Figure 7**) was significantly decreased ($p<0.05$) in CRS induced group (positive group) as compared to the PLE groups and the negative control (induced but not treated). Treatment with PLE significantly elevated dopamine level in a dose-dependent manner as compared with positive control group ($p<0.05$), and in dexamethasone

treated group (the reference group) which had the highest concentration of dopamine.

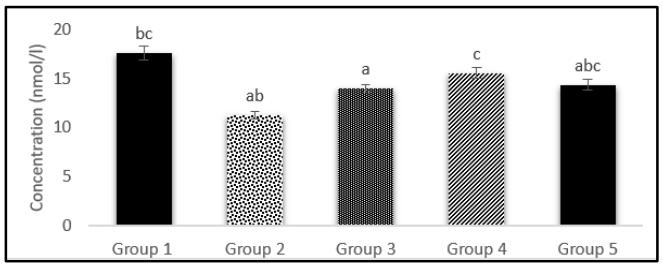

Figure 7: Effects of PLE on the dopamine concentration of in neurological dysfunction wistar rats. Results were presented as mean±standard deviation where n=5. Values with different superscripts are significantly different (p≤0.05).

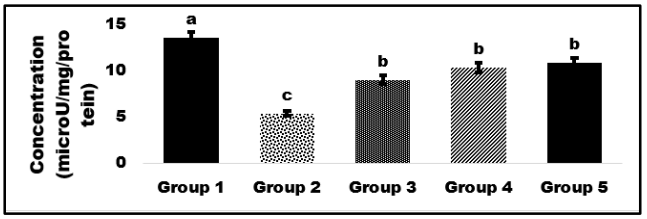

Figure 8: Effects of PLE on the acetylcholineterase activity of in neurological dysfunction wistar rats. Results were presented as mean±standard deviation where n=5. Values with different superscripts are significantly different (p≤0.05).

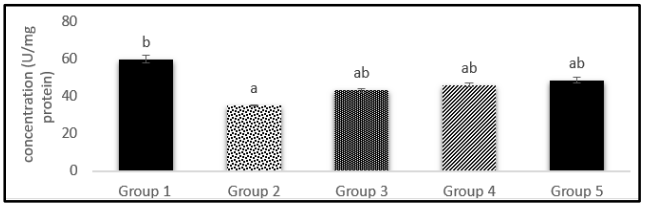

Figure 9: Effects of PLE on the tyrosine hydroxylase activity of in neurological dysfunction wistar rats. Results were presented as mean±standard deviation where n=5. Values with different superscripts are significantly different (p≤0.05).

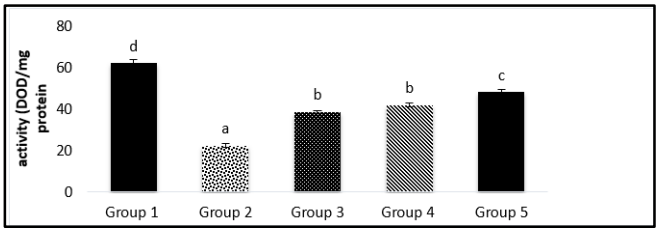

Figure 10: Effects of PLE on the NADH-Ubiquinone dehydrogenase activity of in neurological dysfunction wistar rats. Results were presented as mean±standard deviation where n=5. Values with different superscripts are significantly different (p≤0.05).

The activity of aceylcholinesterase, was revealed in **Figure 8**, there was a significant increase (p<0.05) in the activity of aceylcholinesterase in the brain in rotenone induced rat. PLE treated groups significantly increased the cholinergic transmission impaired by the rotenone (p<0.05). **Figure 9** revealed the activity of tyrosine hydroxylase, it was shown that, there was a significant decrease (p<0.05) in the activity of tyrosine hydroxylase in the brain of CRS-induced rats group (positive control group), compared to the experimental groups. Treatment with PLE significantly elevated the activity of tyrosine hydroxylase in a dose-dependent manner (p<0.05). Effects of CRS-intoxication and PLE dose-dependent treatment on the activity of complex-I enzyme was revealed in **Figure 10**. The result showed that there was a significant decrease (p<0.05) in the activity of NADH-Ubiquinone dehydrogenase in the brain of CRS-induced neurotoxic rats (positive control group), treatment with PLE significantly (p<0.05) elevate NADH-Ubiquinone dehydrogenase activity in a dose-dependent manner compared to the CRS-induced neurotoxic rats.

3.5. Behavioural index test

The result of the spatial working memory test (Y- Maze) in the wistar rats after an exposure to CRS and *P. niruri* leaf extract, the percentage alteration between the arms A, B and C of Y-maze was evaluated. **Figure 11** revealed the effects of *P. niruri* leaf extract on the alternation output in the brain of CRS-induced neurotoxic rats. There was a significant decrease in the spatial working memory using Y-maze test in CRS-induced but not treated rats group (positive control group), when compared to the rats without induction (negative control group) (p<0.05). Administration of *P. niruri* leaf extract showed a dose-dependent significant increase (p<0.05) in the spatial working memory using Y-maze test by improving the rats memory to explore its new environment when compared to the CRS-induced neurotoxic and untreated group, also administration of prazosin was able to significantly increase (p<0.05) the spatial working memory using Y-maze test when compared to the CRS-induced neurotoxic group (positive control group).

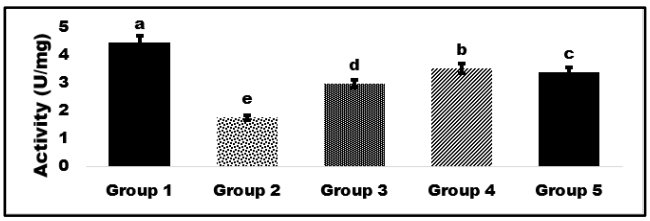

Figure 11: Effects of PLE on Y-maze task in the brain on CRS induced neurological dysfunction in wistar rats. Results were presented as mean±standard deviation where n=5. Values with different superscripts are significantly different (p≤0.05).

4. Discussion

Phytomedicine is becoming increasingly accepted as a viable alternative to conventional medicine, thanks to rigorous clinical and preclinical studies. The therapeutic effects of phytomedicine stem from the bioactive compounds found in plants, which interact with biological systems to produce

specific physiological responses.[9] Different part of plants such as the leaves, roots, stem, bark and the fruits have been reported to be rich in phytochemicals that are of nutritional and health benefits to man. The healing or protective effect of these plants against disease such as diabetes, cancer, infection and neurological disorders is attributed to various activities of their phytochemical constituents.[10] *Phyllanthus niruri* L. (Euphorbiaceae) is a prevalent tropical plant with recognized medicinal properties. It is widely used as ethnomedicine for the remedy of inflammation, hepatitis, fever, malaria, and gonorrhoea, in many parts of the world like Brazil, Asia, Thailand, China and Africa.[6] The biological and pharmacological functions reported for *P. niruri* include antiplasmodial, antioxidant, hepatoprotective, nephroprotective and anti-diabetic properties.[11] Scientific investigation also report that *Phyllanthus niruri* has potent activity against various diseases such as hepatitis B, HIV, microbial infections, diabetes, nephrotoxicity, hepatotoxicity, and biological oxidation. A report on the phytochemical analysis of *Phyllanthus niruri* linked the presence of the phytochemicals to the various pharmacological activities in which antioxidant activity was connected to the presence of flavonoids, antispasmodic activity to alkaloids, and antiplasmodial activity to lignans.[6]

The brain relies entirely on glucose as its primary energy source and requires oxygen to fully convert glucose into energy. Since both glucose and oxygen are delivered to the brain through the bloodstream, a continuous blood supply is crucial for maintaining proper brain function. Shortage of these supplies as a result of disturbances in normal blood flow to the brain from short-to-long-term resulted in cell damage or death and generally referred to as stroke.[12] Brain function in controlling and coordinating various activities in the body makes it one of the complex organs in the human body. It is made up of neurons, which are involved in sending and receiving signals, microglia and astrocytes that ensure proper functioning of neurons.[13] With this crucial function, it is surprising that the brain is one of the organs with the lowest antioxidant defense system. Neuropathology of the brain can be in the form of cerebrovascular and neurodegenerative disease.[14] Many neurological diseases, such as brain injury, stroke, Alzheimer disease and Parkinson's disease can be severely functionally debilitating in nature. Na^+-K^+ ATPase is a pump that couples the active exchange of three intracellular Na+ ions for two extracellular K^+ to the hydrolysis of a molecule of Adenosine triphosphate (ATP), and it is so important because almost a third of the ATP molecules generated by the mitochondria in animal cells are used to run this pump. Its activity depends on the integrity of the cell membrane structure. It has been reported to decrease in mammalian tissues under oxidative stress assault, possibly because of the structure and function affected by oxidative stress.[15] In this study, treating rats with an increasing dose of PE increased activity in a dose-dependent manner. The antioxidant-enhancing capability has been linked to the increase in the activity of this enzyme.

Neuroinflammation is thought to play a key role in the neurodegeneration that occurs with aging. It's a natural aspect of aging and has been linked to the development of age-related neurological disorders, including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.[16] Inflammation normally acts as a defense response of the body. However, the dysregulation of inflammation can transform it into a destructive force that results in a plethora of events, subsequently leading to neuronal death.[17] Stimulation of myeloperoxidase, an inflammatory enzyme has being reported to augments ROS production.[18] Thus, there seems to be interplay between neuroinflammation and oxidative stress, which could perpetuate the phenomenon of neurodegeneration through activation of apoptosis.[19] Myeloperoxidase (MPO) and the proinflammatory enzyme also reported to be an excellent marker for brain injury and evidences abound of its damaging role in models of PD[20] MPO-dervied chlorimated compounds are specific biomarkers for disease progression. TNF-α, IL-1β, IL-6 and xanthine oxidase oxidizes chloride through MPO production of hypochlorous acid (HOCL) then the excessive production of these radicals can cause oxidative stress leading to oxidative tissue injury. In this study, it was observed that *p. niruri.* reduced the level of MPO produced in the brain of rats, thereby control the production of HOCL which may result in oxidative stress and oxidative tissue injury.

The effect of *P. niruri.* Leaf extract on CRS induced neurotoxicity on the pro-inflammatory assay, showed an obvious inflammation response TNF-α, IL-6, and IL-1β during induction. NF-κB is a critical factor for the expression of various pro-inflammatory cytokines, such as TNF-α, IL-6 and IL-1β.[21] Suppression of NF- can lead to the reduction of pro-inflammatory cytokines, thus modulate the inflammatory process. Inflammation mediator NO is produced by iNOS and involved in many biological functions. Overexpression of iNOS is associated with inflammatory responses and serious disorders such as septic shock and rheumatoid arthritis.[22] This study showed that the levels of TNF-α, IL-6, and IL-1β were significantly decreased in *p. niruri.* treated groups.

Neuroprotection can be defined as the process and mechanism involved in preventing neuronal injury as a result of acute and/or chronic neurodegenerative diseases. Current research on the etiology of several neurodegenerative diseases has recognized mitochondrial and proteasome dysfunction as well as oxidative stress as major factors. From the result obtain from the research *p. niruri.* treated groups drastically showed increased in the enzyme activity by inhibiting the effect of CRS in all the neurological assay carried out (dopamine, aceylcholinesterase, tyrosine hydroxylase and NADH-Ubiquinone dehydrogenase), also the importance of neuro-behavioural studies in risk assessment lies in the fact that behaviour can be regarded as the net output of the sensory, motor and cognitive functions occurring in the nervous system and can serve potentially as

sensitive end points of chemically induced neurotoxicity. Several studies suggested a general decline in learning abilities mediated by rotenone toxicity. The present study assessed the effect of *p. niruri.* leaf extract on CRS induced neurotoxicity, the treatment were effective in preventing anxiety-like motor activities and behaviors observed in both Y-maze test and light and dark box test, The observation showed that rats that were not treated with *p. niruri.* exhibited poor coordination and memory performances. In addition, sensory deficits were evident in those rats, such as visual problems. While the pretreated groups showed an enhancement in the spatial memory function and also in their behaviour when compared to the normal control. These results shows that *P. niruri.* Leaf extract has the potential component for the management neurological dysfunction (learning and memory).

5. Conclusion

CRS has adverse effects health. The present study had revealed that CRS is capable to cause marked alterations in some behavior and biochemical parameters by inducing oxidative damage by inhibiting the antioxidant enzymes activities. Whereas the administration of *P. niurri* minimize the hazard caused by CRS induction. In addition, *P. niurri* proved to be beneficial in decreasing free radicals showed at the result obtained. Consequently, CRS exposure should be reduced by paying more attention to its sources.

6. Conflict of Interest

There is no conflict of interest

7. Source of Funding

None.

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