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Original Article

Polyherbal Therapy Restores Sensorimotor Function in Chronic Stress-induced Oxidative Damage

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ABSTRACT

Introduction: Stress is a mental strain resulting from adverse circumstances. One of the main predictors of the onset of a major depressive episode is chronic, mild stress. Oxidative stress is caused by an imbalance between the production of reactive oxygen species (ROS) and the body's ability to remove them through antioxidant defenses. This imbalance in sensorimotor function may have a substantial effect on both motor output and sensory processing. This study evaluates the impact of polyherbal formulation (PHF) on sensorimotor function under unpredicted mild chronic stress (UCMS).

Materials & Methods: A total of 25 adult Wistar rats (120-150 g) were divided at random into five groups consisting of five animals each. Rats in group 1 received 1 mL of distilled water each; group 2 was exposed to UCMS; group 3 was exposed to UCMS and treated with imipramine (25 mg/kg); groups 4 and 5 were exposed to UCMS and received PHF extract (250 mg/kg and 750 mg/kg), respectively. All groups received oral treatment once daily for 21 days. Animals were subjected to a beam-walking task to assess sensorimotor function following 21 days of treatment. Following behavioral tests, the animals' cervical dislocation was followed by histological examination of the cerebellum and biochemical estimation of the activities of corticosterone, malondialdehyde (MDA), and catalase (CAT).

Results: Using Lorke's method, the LD_{50} of PHF was determined to be 2500 mg/kg. A significant improvement in motor deficits was suggested by the treatment groups' significantly lower beam-walking time ($P<0.05$), significantly lower levels of corticosterone and MDA ($P<0.05$), and significantly higher levels of CAT ($P<0.05$). Furthermore, moderate healing with active Purkinje cells and mild degeneration of granular cells in the histological section of the treated groups was observed.

Conclusion: Conclusively, treatment with PHF enhanced sensorimotor functions and mitigated oxidative damage due to stress.

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1. Introduction

Mental illnesses are a global health issue [1]. World Health Organization (WHO) statistics indicate that approximately 450 million people worldwide suffer from mental illnesses [2]. With mood disorders as a whole constituting the most commonly diagnosed condition, major depressive disorder (MDD) is the most prevalent psychiatric conditions [3]. An estimated 264 million people worldwide suffer from MDD, which is the leading cause of suicide and contributes to the global burden of disease [4]. The prevalence of depression increased by 18% worldwide between 2005 and 2015, and the number of cases is growing at an alarming rate [3].

One of the main predictors of the onset of a major depressive episode is chronic mild stress (CMS), which is commonly mentioned in the literature [5]. The pathophysiology of MDD includes alterations in the oxidative and inflammatory pathways [6, 7]. Myeloperoxidase (MPO), whose expression is increased in depressed individuals, and interleukin 6 (IL-6) are two molecules linked to oxidative and inflammatory processes. The use of quetiapine therapies alters MPO activity. These changes might be temporary, with a decrease in amygdala activity, or a reduction in hippocampus and prefrontal cortex function [6]. IL levels in arthritic mice were also assessed and quetiapine was found to possess anti-inflammatory effect [8]. Sensorimotor function—the integration of sensory and motor output—constitutes a fundamental aspect of human cognition and behavior. It is how the nervous system acquires, interprets, and uses sensory information for the control of motor processes [9]. Integration of sensory and motor information occurs at several levels of the nervous system. Higher-order motor planning areas are some of the most critical areas where pathological alterations may be observed. Because sensorimotor operations are so central to early life, this type of involvement is developmentally significant.

Infants learn primarily through perceptual exploration and motor interactions with their surroundings during the sensorimotor stage (0–2 years) according to Piaget's developmental theory [10].

Oxidative stress is caused by an imbalance between the production of reactive oxygen species (ROS) and the body's ability to remove them through antioxidant defenses. This imbalance may affect sensorimotor function and have a substantial effect on both motor output and sensory processing [11].

The goal of the current study is to examine how polyherbal formulation (PHF), affects sensorimotor function in Wistar rats under oxidative stress caused by unpredictable chronic stress. The knowledge gained from this study may improve occupational medicine, healthcare delivery, and key mechanisms of stress-related motor dysfunction [12].

2. Materials and Methods

2.1. Research design

Twenty-five healthy female Wistar rats, weighing between 120 and 150 g, were obtained from the Alex Ekwueme Federal University Animal Farm in Ndufu-Alike, Ebonyi State, Nigeria (AE-FUNAI), at the age of six months. After being housed in ventilated wire cages for 14 days, the rats were divided into five treatment groups at random. All the animals were kept in carefully regulated lab settings with a 12-hour day-night cycle, an ambient temperature of 23±2 ˚C, and a relative humidity of 50±5%. Rodents' standard chow (Vital Feeds Nigeria Ltd., Jos) and water were freely available. The experiment was conducted according to the guidelines of the Institute of Laboratory Animal Resources (ILAR) [13] for the care and use of laboratory animals.

2.2.1. Plant collection and identification

On November 17, 2024, Thyme (*Thymus vulgaris*), Rosemary (*Salvia rosmarinus*), Beetroot (*Beta vulgaris*), *Praxelis clematidea*, and *Lantana camara* were all gathered and identified from a local market in Abakaliki, Ebonyi State, Nigeria. A plant taxonomist at the University of Uyo's Department of Pharmacy confirmed the botanical identity of *L. camara* leaves using reference specimens kept in the university herbarium (Voucher number: UUPH17AI).

2.2.2. Preparation and extraction of the plant extract

After being washed in running water, the plants were chopped into smaller pieces to aid in drying. Using a mechanical machine, the freshly chopped plants were ground into powder after being air-dried at room temperature in the shade with active ventilation. The Mettler Toledo electronic scale was employed for weighing 100 g portions of finely powdered *T. vulgaris*, *S. rosmarinus*, *B. vulgaris*, *P. clematidea*, and *L. camara* (Table 1). Moreover, the Mettler Toledo electronic scale was used to weigh a 250 g portion of finely ground *L. camara* powder. After combining the finely ground ingre-

Table 1. Composition of PHF

Botanical name	Family	Part Used	Weight (g)
T. vulgaris	Lamiaceae	Flower	100
S. rosmarinus	Lamiaceae	Leaves	100
B. vulgaris	Amaranthaceae	Root	100
P. clematidea	Asteraceae	Leaves	100
L. camara	Verbenaceae	Leaves	250

dients in a 2:1:1:1 ratio, they were dissolved in 60 mL of distilled water and 2.5 L of 70% methanol. After a 72-hour maceration in the solvent, extraction was performed, and homogeneous filtrates were obtained by filtering through Whatman grade 1 filter paper. There were two phases to the concentration process: Primary rotary evaporation at 45 ˚C and secondary evaporation in open dishes on a water bath with temperature control. The final stock solution was prepared using distilled water as the solvent and had a concentration of 100 mg/mL (1 g/10 mL).

2.3. Acute toxicity study (LD_{50})

By Lorke's established protocol [14], 15 animals were divided into five treatment groups (three animals per group) for dose-range testing. PHF was administered orally in doses ranging from 1000 to 5000 mg/kg. Daily observations were conducted for 14 days following continuous monitoring for immediate reactions during the first hour post-dosing). No toxicological or mortality symptoms were observed at any dose level.

2.4. Unpredictable chronic mild stress

By changing the stressors, we modified Duccoted's chronic stress protocol. Eight different modalities were included in our stress battery: Physical restraint, forced swimming in warm water (30 ˚C), food deprivation, acoustic stimulation, damp bedding exposure, water restriction, and undisturbed control condition. To avoid habituation, the stressors were presented according to a randomized schedule with varying durations [15].

2.5. Experimental design

Throughout the experimental period, daily oral administration was carried out for the following groups:

Group 1: Vehicle control (distilled water, 1 mL, oral)

Group 2: Unpredicted mild chronic stress (UCMS) - only group (untreated)

Group 3: UCMS + standard drug (imipramine 25 mg/kg, oral)

Group 4: UCMS + PHF (250 mg/kg, oral)

Group 5: UCMS + PHF (750 mg/kg, oral).

2.6. Narrow beam-walk

On day 21 (8:00–10:00 AM), 60 minutes after the final PHF administration, the beam walking test was carried out. Following predetermined procedures, animals were trained to cross a raised wooden beam 1 m high and 2.5 cm wide [16, 17]. Measurements of (a) traversal latency (time to cross) and (b) foot faults (occurrences where limbs contacted beam sides or slipped off the surface) were recorded for each session, which consisted of three consecutive trials. Faults were defined as any departure from typical plantar stepping, and final scores were the average values across all trials.

2.7. Animal sacrifice and sample collection

On day 22 (9:00–10:00 AM), whole brains were removed following cervical dislocation euthanasia and preserved in physiological saline. Using a motor-driven Teflon homogenizer, homogenates were prepared in 0.1 M phosphate buffer (pH 7.0). Cold centrifugation was then performed for 15 minutes at 4 ˚C and 3000 rpm. The supernatant was separated and kept at -80 ˚C until biochemical tests were completed.

2.8. Biochemical assay

2.8.1 Determination of lipid peroxidation

Wills' spectrophotometric method was used to quantitatively analyze malondialdehyde (MDA), an end product of lipid peroxidation [18].

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Table 2. Acute toxicity screening of PHF

Group (n=3)	Dosage (mg/kg)	Mice Mortality
Group 1	3000	0/3
Group 2	4000	0/3
Group 3	4500	0/3
Group 4	5000	3/3

2.8.2. Determination of catalase (CAT) activity

The enzymatic activity of CAT was measured by measuring the rate of hydrogen peroxide decomposition at 240 nm using the spectrophotometric protocol developed by Aebi [19].

2.8.3 Assay of corticosterone

Using ferric iron (Fe^{3+}) and modifying Singh and Verman's principle [20], corticosteroids were oxidized in an acidic medium. The reaction between ferrous iron (Fe^{2+}) and potassium hexacyanoferrate (III) produced a colored complex.

2.8.4. Histopathological studies

Histopathological analysis was conducted on the brain, particularly the hippocampus and hypothalamus. In each group, one sample was collected and preserved in 10% formalin, and the cerebellum was separated for histological examination.

2.9. Statistical analysis

Results are presented as Mean±SEM. Statistical significance was determined using one-way ANOVA followed by Tukey's post hoc test (GraphPad Prism software, version 8.0), with $P<0.05$ considered statistically significant.

3. Results

3.1. LD_{50} of PHF

The acute toxicity profile of PHF, as established by Lorke's method, is shown in Table 2. Based on the experimental series, the computed LD_{50} was 2500 mg/kg (oral administration), falling between the highest non-lethal dose and the lowest lethal dose.

3.2. Neurobehavioral evaluation of beam walking time

Significant changes in beam walking crossing times between experimental groups are shown in Figure 1. Crossing times were noticeably longer in the UCMS-exposed group ($P<0.05$ compared to control). Compared

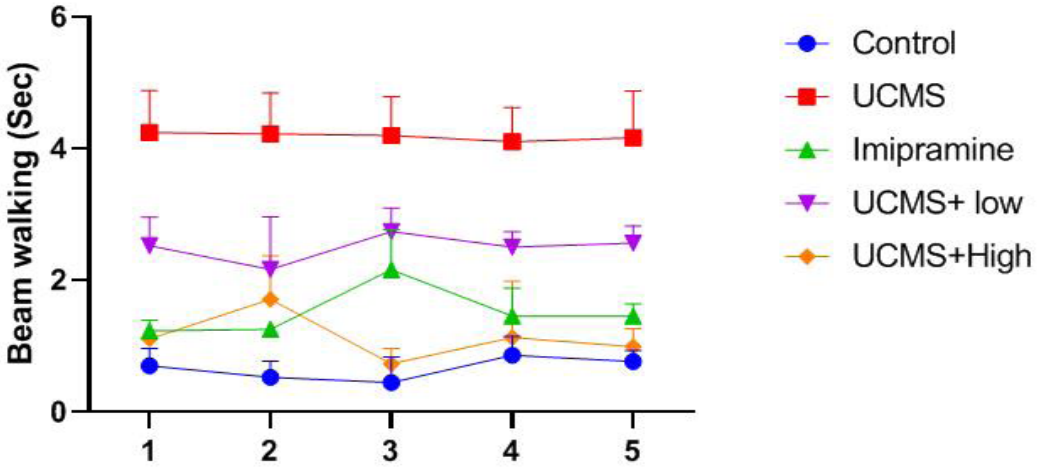

Figure 1. Effect of PHF on beam walking time in beam walking task

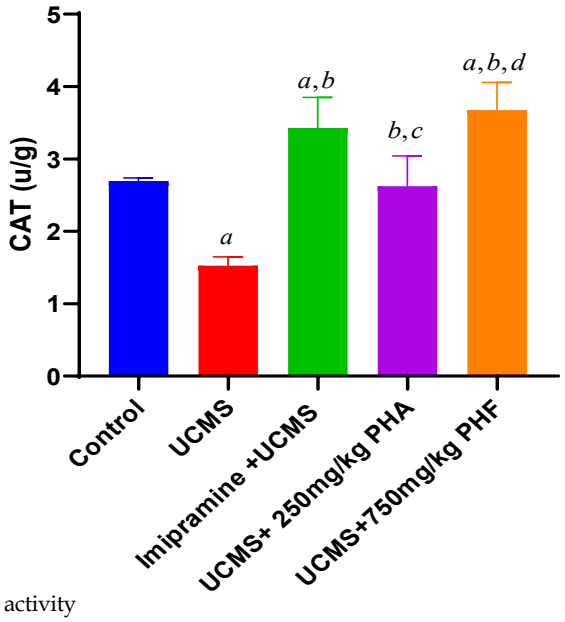

Figure 2. Effect of PHF on CAT activity

[a]Positive control (P<0.05), [b]UCMS group (P<0.05), [c]Imipramine group (P<0.05), [d]PHF low dose (P<0.05).

Note: Data are presented as Mean±SEM, using one-way ANOVA followed by Turkey post hoc test, with n=5.

to controls, the imipramine-treated and high-dose PHF groups exhibited significantly shorter latencies (P<0.05). All treatment groups (imipramine, low- and high-dose PHF) demonstrated significantly improved performance compared to the UCMS group (P<0.05).

3.3. Evaluation of CAT activity

In Figure 2, CAT activity showed notable differences among groups. Compared to controls, the UCMS, imipramine, and high-dose PHF groups exhibited lower CAT activity (P<0.15). In contrast, low dose PHF treatment resulted in higher CAT activity than controls (P<0.05). Both imipramine and high-dose PHF treatments increased CAT activity relative to the UCMS group (P<0.05).

3.4. Evaluation of corticosterone level

Corticosterone levels varied significantly among experimental groups, as shown in Figure 3. Compared to controls, the UCMS group showed elevated corticosterone levels (P<0.05). Although all treatment groups (imipramine, low- and high-dose PHF) showed higher corticosterone levels than controls (P<0.05), they also demonstrated significant reductions relative to the UCMS group (P<0.05).

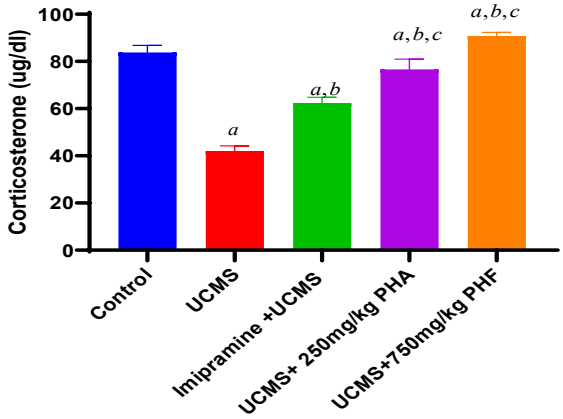

Figure 3. Effect of PHF on corticosterone level

[a]Positive control (P<0.05), [b]UCMS group (P<0.05), [c]Imipramine group (P<0.05).

Note: Data are presented as Mean±SEM, using one-way Anova followed by Turkey post hoc test, with n=5.

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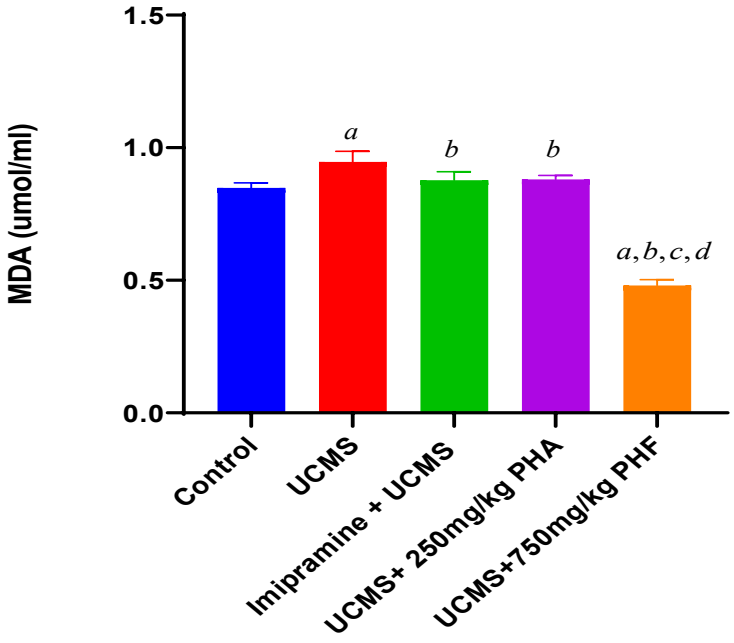

Figure 4. Effect of PHF on MDA level

[a]Positive control (P<0.05), [b]UCMS group (P<0.05), [c]Imipramine group (P<0.05), [d]PHF low dose (P<0.05).

Data are presented as Mean±SEM, using one-way ANOVA followed by Turkey post hoc test, with n=5.

3.5. Evaluation of MDA activity

MDA levels are presented in Figure 4. The results demonstrated a significant decrease in MDA levels in the UCMS and high-dose PHF groups compared to the control group (P<0.05). Conversely, imipramine, low-dose PHF, and high-dose PHF treatments resulted in a significant increase in MDA levels relative to the UCMS group (P<0.05).

3.6. Histology of the cerebellum

Figure 5 shows the histological staining of the cerebellum. The photomicrograph of the cerebellum from control animals, provided with feed and water, reveals a well-defined cerebellar cytoarchitecture, including the molecular layer (ML), Purkinje layer (PL), granule cell layer (GCL), cerebellar glomerulus (circle), Bergmann glial cells (arrowhead), and Purkinje cells (arrows). Photomicrograph from cerebellum of group 2 animals exposed to stress reveals hypoplastic Purkinje cells (arrows), distorted cerebellar architecture (double arrow), spindle-shaped Purkinje cell (arrowhead), and a reduced granule cell population (star). In contrast, the photomicrograph of cerebellum from group 3 animals, exposed to stress and treated with 25 mg/kg of the standard drug shows regularly shaped Purkinje cells (arrows). The photomicrograph of cerebellum from group 4 animals, exposed to stress and treated with 250 mg/kg of extract (low dose), shows regularly shaped Purkinje cells (arrows), along with a few spindle-shaped Purkinje cells (arrowhead). In group 6 animals, exposed to stress and treated with 750 mg/kg of extract (high dose), the photomicrograph of cerebellum reveals regularly shaped Purkinje cells within the Purkinje cell layer (arrows).

4. Discussion

In the present study, we have evaluated the effect of PHF on sensorimotor function in oxidative stress induced by chronic unpredictable stress in Wistar rats. Herbal medicines were utilized for this study owing to their long-standing use in treating neuropsychiatric and oxidative stress disorders [21]. The plants employed in the current study show that *T. vulgaris*, *S. rosmarinus*, *B. vulgaris*, *P. clematidea*, and *L. camara* exhibit antioxidant, anti-inflammatory, and neuroprotective effects as reported by traditional systems of medicine. Since oxidative imbalance and neuroinflammation play a central role in MDD pathogenesis, PHFs with potent antioxidant phytochemicals can be therapeutically beneficial [22]. Herbal components' phytochemicals act synergistically through more than one mechanism and therefore are suitable for complex conditions like depression and sensorimotor dysfunction. The LD_{50} is one way to measure the acute toxicity of a substance. An acute toxicity study was conducted to evaluate the safety of PHF methanol

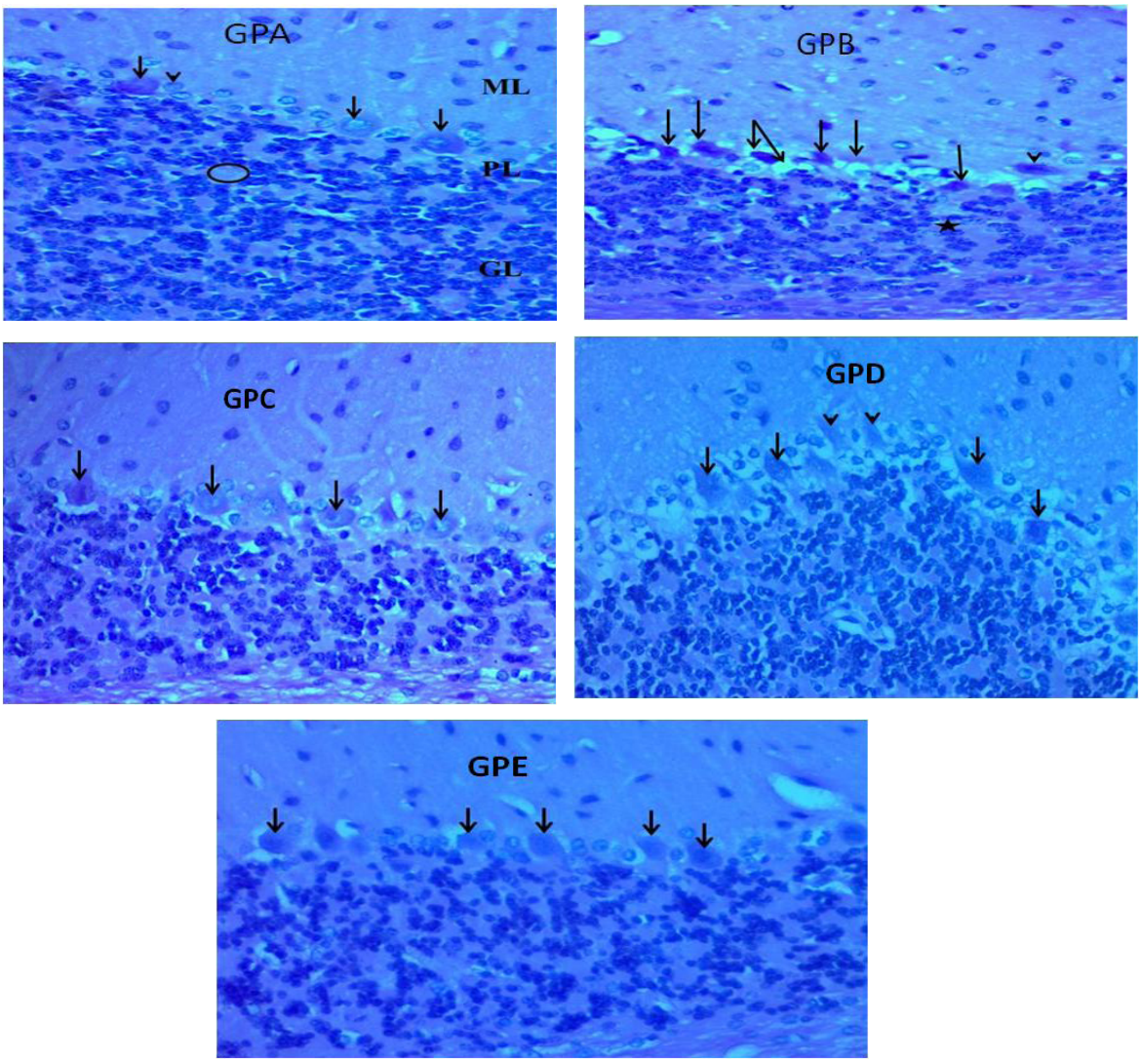

Figure 5. Photomicrograph of cerebellum (Haematoxylin and eosin, ×40 magnification)

Note: GPA: Group 1; GPB: Group 2: GPC: Group 3; GPD: Group 4; GPE: Group 5.

extract and its fractions. The study performed an acute toxicity test (LD_{50}) in accordance with Lorke's method, and arrived at the conclusion that the oral LD_{50} of PHF is 2500 mg/kg. Based on this, two doses (750 mg/kg and 250 mg/kg) were selected for this study. It was found that no signs of toxicity or mortality was observed in mice receiving PHF extract up to 2500 mg/kg.

The beam walking test evaluates sensorimotor function and balance by recording the time it takes for an animal to cross a narrow beam. The decrease in the beam walking time in the PHF high dose group suggests an improvement in the impairment that causes disabilities affecting mobility and motor coordination. In models of oxidative stress or neurological damage, such as those induced by chronic stress, increased beam walking time generally indicates impaired motor coordination. *B. vulgaris* has been studied for its potential neuroprotective effects, especially in the context of oxidative stress, due to its rich antioxidant content, particularly nitrates and betalains. Studies using *B. vulgaris* extract have shown it can reduce oxidative damage, thus potentially improving motor functions and decreasing beam walking time. Clifford et al. [23] found that beetroot supplementation improved motor performance by reducing biomarkers of oxidative stress in rat models. Another study noted that beetroot supplementation in rodents improved sensorimotor performance and reduced inflammation [24]. These findings suggest that PHF could help improve motor function by protecting neurons from oxidative stress.

CAT is an essential antioxidant enzyme in the body that breaks down hydrogen peroxide into water and oxygen, mitigating the damaging effects of oxidative stress,

which is particularly relevant in tissues associated with motor and cognitive functions, thereby protecting cells from oxidative damage. In this study, there was an increase in CAT activity following the administration of PHF. PHF can enhance the expression and activity of CAT by scavenging free radicals, thus reducing oxidative stress. In sensorimotor functions, oxidative stress can damage neuronal pathways and disrupt normal neural signaling, impairing coordination, movement, and response to stimuli. Studies indicate that *S. rosmarinus* supplementation can elevate CAT activity in neural tissues, helping reduce oxidative damage [25]. Enhanced CAT activity prevents excessive buildup of ROS, maintaining cellular integrity, which is essential for preserving motor function and overall sensorimotor performance. For example, in animal models exposed to neurotoxic agents or chronic stress, rosemary extract has been observed to improve motor coordination, reduce anxiety-like behavior, and protect sensorimotor pathways, with increased CAT levels partially explaining these protective effects [26].

Elevated corticosterone levels due to chronic stress can impair cognitive and motor functions, leading to oxidative damage in brain regions responsible for sensorimotor coordination. Research suggests that *T. vulgaris* can influence the hypothalamic-pituitary-adrenal (HPA) axis, specifically by affecting levels of corticosterone, a glucocorticoid released in response to stress in animals (analogous to cortisol in humans). Research suggests that *T. vulgaris* can influence the HPA axis, specifically by affecting levels of corticosterone, a glucocorticoid released in response to stress in animals (analogous to cortisol in humans). Studies indicate that *T. vulgaris* may help regulate corticosterone levels, potentially protecting against stress-induced neurotoxicity and promoting healthier sensorimotor function. In animal models, *T. vulgaris* extracts have been shown to reduce corticosterone levels under stress, likely due to their antioxidant and anti-inflammatory properties, which mitigate oxidative damage in brain regions critical for motor coordination and sensory processing [27]. Lower corticosterone levels in the treatment groups administered with PHF are associated with reduced neuroinflammation and preservation of neuron health, contributing to better performance in motor tasks and overall sensorimotor function [27].

MDA is a marker of lipid peroxidation and oxidative stress, with high levels indicating increased cell membrane damage, particularly in neural tissues. Excessive oxidative stress can impair sensorimotor functions by damaging neurons, which are crucial for coordinating sensory inputs with motor outputs. *P. clematidea*, a plant known for its anti-inflammatory and antioxidant properties, has gained attention for its potential neuroprotective effects, partly due to its impact on MDA levels. *P. clematidea* may help lower MDA levels, thus reducing oxidative stress in brain regions involved in sensorimotor control. By decreasing lipid peroxidation and reducing MDA levels, *P. clematidea* could preserve neural integrity and protect against damage caused by ROS. Animal studies consistent with the findings of this research on PHF have shown that administering *P. clematidea* extracts can lead to reduced MDA levels, which correlate with improved sensorimotor functions, including enhanced balance, coordination, and responsiveness to stimuli [27].

5. Conclusion

In conclusion, the study evaluated a novel PHF of five plants that had not previously been studied together for mental illness and oxidative stress. Whereas most herbal research focused on mood or behavior, this study examined sensorimotor function in the context of oxidative stress, an under-researched aspect of depression research. The findings of this study demonstrate that PHF exerts protective effects on sensorimotor function in Wistar rats exposed to oxidative stress induced by chronic stress. By modulating the HPA axis, reducing oxidative stress, and providing neuroprotection, PHF significantly improved motor coordination and sensorimotor function. These results suggest that PHF could be a promising therapeutic intervention for managing oxidative stress-related motor dysfunctions and may offer a natural remedy for stress-induced neurodegeneration.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Animal and Ethics Committee of Alex Ekwueme Federal University (Ndufu Alike), Ikwo, Nigeria (Code: AEFUNAI 2025/00345).

Data availability

The corresponding author can provide the datasets created and/or examined during the current study upon reasonable request.

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Authors' contributions

Methodology, formal analysis and investigation: All authors; Conceptualization, writing and supervision: Uduak A. Inwang.

Conflict of interest

The authors declared no conflict of interest.

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