**Evaluation of Antiparkinsonian Activity of Methanol Leaves Extract of *Mucuna pruriens* in Haloperidol-induced Parkinson’s disease**

**ABSTRACT**

**Background:** Parkinson's disease is the second most common neurodegenerative condition. It is characterized by the destruction of dopaminergic neurons in the substantia nigra of the striatum, resulting in a decrease in dopamine (DA) levels. *Mucuna pruriens*, commonly known as velvet bean, has a long history of use in traditional medicine, particularly in Ayurveda. It has been utilized for various purposes, including as an aphrodisiac, a nervine tonic, and for treating Parkinson's disease and other nervous system disorders. *Mucuna pruriens*, known as Kiwach in Hindi, is called Atmagupta in Sanskrit. Among the Yoruba tribe in southwestern Nigeria, it is referred to as werepe. The plant belongs to the Fabaceae family and the Papilionaceae subfamily. While most previous research has focused on the seeds of this plant, we have chosen to investigate its leaves. This study aims to analyze the antiparkinsonian activity of the methanolic leaf extract of Mucuna pruriens (MLEMP).

**Materials and Method:** Catalepsy test, rotarod test, exploratory behavior test (rearing) and locomotor activity tests were conducted to observe antiparkinsonian activity of the MLEMP (200, 400, 800 mg/kg) in haloperidol-induced Parkinson’s disease using rats.  The levels of malondialdehyde (MDA) and reduced glutathione (GSH) in the brain's striatum were measured to assess oxidative stress.

**Results:** MLEMP pretreated groups showed a significant decrease in the latency period in the catalepsy test (p < 0.05) and a significant increase in retention time in the rotarod test (p < 0.05) compared to the haloperidol-treated group alone. The MLEMP-pretreated groups demonstrated a significant antioxidative effect, shown by a marked increase in GSH levels (p < 0.05) and a reduction in brain MDA levels (p < 0.05).

**Conclusions:** In the pathophysiology of Parkinson's disease (PD), oxidative stress plays a crucial role. The results of this study demonstrate that MLEMP exhibits antioxidant activity and provides neuroprotective effects in the haloperidol experimental model of PD.

*Keywords: Mucuna pruriens, Haloperidol, Anti-oxidant, Glutathione, Malondialdehyde.*

1. **INTRODUCTION**

“Parkinson's disease is a progressive neurodegenerative disorder characterized by both motor and non-motor symptoms” (Hayes, 2019; Malaiwong et al., 2019). “The prevalence of Parkinson's disease increases with age, affecting approximately 1–3% of individuals over 60 years old globally” (Ball et al., 2019). “One of the causes of Parkinson's disease is the use of antipsychotic drugs, leading to a condition known as Drug-Induced Parkinsonism. This occurs due to extrapyramidal side effects caused by the blockade of dopamine receptors” (Grubor et al., 2020). “Clinically, this condition is characterized by symptoms such as akinesia, tremors, bradykinesia, muscle rigidity, and postural instability, which can appear within days or weeks after starting antipsychotic medication” (Erjavec et al., 2022). “Drug-induced Parkinsonism is the second most common cause of Parkinson's disease in the elderly” (Kabra et al., 2020). “It is also the most prevalent type of Parkinsonism in the working-age population, with cases identified in individuals as young as 39 years old. DIP accounts for 11 out of 15 cases of Parkinsonism” (Jeong et al., 2021). “Haloperidol is a typical antipsychotic that has stronger extrapyramidal effects compared to atypical antipsychotics. The increase in Parkinsonism driven by these extrapyramidal effects may elevate the prevalence of Parkinson's disease among the working-age population in Africa. In psychiatric treatment, antimuscarinic antiparkinsonian medications are commonly used to alleviate extrapyramidal motor symptoms caused by neuroleptic antipsychotic drugs. When used alongside antipsychotics, antimuscarinic antiparkinsonian agents have been reported to counteract the therapeutic effects of neuroleptics. Additionally, several reports indicate that these agents can induce various psychotic syndromes, elevate mood, create stimulant effects, and lead to stereotypy, dyskinesia, and behavioral agitation. Extensive data have shown that antimuscarinic antiparkinsonian medications also act as strong indirect dopamine agonists” (Vaiman et al., 2022). There is a need for safe alternatives to antiparkinsonian medications to be used as adjunct therapy for patients with psychotic disorders. Currently, many naturally derived medicines are being researched for their potential benefits in treating Parkinsonism.

*“Mucuna pruriens* is a common weed found in fields, bushes, and fallow farmland. It is native to southern China and eastern India but is also widely distributed in tropical regions, including Nigeria. *Mucuna pruriens* is a vigorous annual climbing legume. Young plants are covered with fine hairs, which disappear as they mature. The leaves are trifoliate, and the flowers are purple. The pods are curved and have longitudinal ribs, while the seeds are black and oval-shaped. Contact with the seeds can cause severe itching on the skin. The plant is used in agriculture to enhance soil fertility” (Gamaniel, 2000). “In ethnomedicine, it is employed to treat various ailments, including enhancing libido and sexual performance, reversing osteoporosis, improving cholesterol levels, and strengthening the immune system” (Prakkash et al., 2001; Malluruwar et al., 2006). The effects observed have been linked to the presence of bioactive compounds, including mucinine, mucunadine, mucunadenine, and pruriendine.

“Additionally, other chemical substances such as lecithin, glutathione, nicotine, L-dopa, and gallic acid, which have been isolated from the plant, may also contribute to these effects” (Guerranti et al., 2001; Raina and Khatri, 2011). In addition, *Mucuna pruriens has* also been reported for its antimicrobial (Patel & Patel, 2015) and antidiabetic activities (Sharma & Jain, 2015). The pharmacological properties of *Mucuna pruriens* have been extensively studied, with the majority of research focusing on the seed extract of the plant. Therefore, this study aims to analyze the antiparkinsonian activity of the methanolic leaf extract of *Mucuna pruriens* (MLEMP).

**2. MATERIALS AND METHODS**

**2.1 Identification and Preparation of Plant Material**

The plant material used for this study was collected from Iwo in Osun State, Nigeria. It was identified at the University of Ilorin Herbarium unit where the voucher specimen was deposited and the voucher number was give as UILH/001/1563/2025. The leaf was washed, dried, and ground into a fine powder. The powdered sample was then stored in an airtight container at 4°C for future experimental use.

**2.2 Preparation of Extract**

A 1000 g powdered sample was extracted using 2.5 L of absolute methanol for 36 hours through the cold maceration method, with occasional stirring. The liquid extract was then filtered using Whatman filter paper No. 1, and the filtrate was concentrated with a rotary evaporator. The concentrated extract was stored at 4°C for future experimental use.

**2.3 Animal Material**

Healthy male Wistar rats (weighing 180-220 g) were obtained from the Animal House of Ladoke Akintola University of Technology in Ogbomosho, Oyo State, Nigeria, for this study. The rats were housed in standard cages, with six animals per cage. They were kept in a temperature-controlled environment (22.5°C ± 2.5°C) and were on a light cycle with the lights on/off routine set for 7 o’clock. The rats had free access to food and water except during behavioral tests. Throughout the experiment, all animals were fed a commercial standard rodent chow that contained 29% protein, 13% fat, and 58% carbohydrate. All regulations regarding animal safety and care were strictly followed.

**2.4 Behavioral Assessment**

Behavioral analyses were conducted on the 7th, 14th, and 28th days of the study, with observations recorded on the 28th day. All groups of rats underwent the following behavioral tests:

**2.4.1 Catalepsy test**

“Catalepsy is a behavioral state observed in rodents where the animals are unable to adjust to externally imposed postures. In this study, haloperidol (1 mg/kg, administered intraperitoneally) was used to induce catalepsy in rats. The duration of catalepsy was measured in seconds using a standard bar test. The bar used for the test was elevated 9 cm above the base. The rat's front paws were placed on this wooden bar, and the time it took for the paws to remain on the elevated bar until they touched the floor was recorded as the cataleptic score. A cutoff time of 180 seconds was applied. The test was conducted on the 28th days of the study” (Aubin et al., 1987).

 2.4.2 **Exploratory behavior (rearing)**

“Rodents exhibit exploratory behavior, such as rearing, when placed in a new environment. During rearing behavior, their forelimbs make contact with the walls of the container. In this study, small individual plexiglass cages measuring 30 × 20 × 30 cm were used for each animal. The rats were allowed a 5-minute habituation period before the test began. After the habituation period, the number of rearing instances was recorded over the next 5 minutes” (Cannon et al., 2009; Aslam et al., 2021).

**2.4.3 Rotarod motor coordination test**

“The Rotarod test was utilized to assess the grip strength and muscle rigidity of all animals involved in the study. This test is a commonly used model for evaluating muscle coordination and motor function. Prior to starting the therapy, each rat underwent training to acclimate them to the Rotarod apparatus. During the test, each rat was placed on a rotating rod set to a speed of 25 revolutions per minute (rpm). A cutoff time of 180 seconds was established for the experiment, and the time until each animal fell was recorded in seconds. The test was conducted on the 7th, 14th, and 28th days of the study” (Aubin et al., 1987).

**2.4.4 Locomotor activity**

“In this study, the locomotor activity of animals was assessed on the 28th days using a digital actophotometer equipped with infrared photocells. The animals' locomotor activity was recorded over a period of 5 minutes, and the results were expressed as counts per 5 minutes” (Sing et al., 2010; Shaheen Khan and Imtiyaz Ansari, 2021).

**2.5 Assessment of oxidative stress**

Oxidative stress was assessed in the striatal region of the brain by estimating malondialdehyde (MDA) and reduced glutathione (GSH).

**2.5.1 Estimation of MDA**

MDA (a marker of lipid peroxidation) was measured as described by Ohkawa et al. Thiobarbituric acid was mixed with the brain homogenate under acidic conditions, and the absorbance of the resulting colour, developed after heating, was measured spectrophotometrically at 535 nm.

**2.5.2 Estimation of reduced glutathione assay (GSH)**

An assay for reduced glutathione was performed by precipitating 1 ml of tissue homogenates with 10% trichloroacetic acid (TCA). Additionally, 0.5 ml of 5,5'-dithio-bis-(2-nitrobenzoic acid) (DTNB) reagent and 4 ml of phosphate buffer solution were added to the homogenized supernatant. The absorbance was measured at 412 nm Aslam and Sial, 2014; Aslam et al, 2021).

**3.0 RESULTS**

**3.1 The Effect of Methanol leaves extract of *Mucuna pruriens* on Exploratory Behavior (rearing) in Rats**

Table 1 revealed that the rearing activity of animals was significantly increased in the groups treated with MLEMP in a dose dependent manner when compared with the haloperidol group.

Table 1: Effect of Methanol leaves extract of *Mucuna pruriens*

|  |
| --- |
| Treatments Doses (mg/kg) Rearing Counts/5 min\*\* |
| Control 0 35.3±0.05  Haloperidol 1 15±0.01  MLEMP 200 20.47±0.09\*  MLEMP 400 27.58±1.17\*  MLEMP 800 38.32±2.12\*  Bromocriptine 2.5 39.54±3.21\* |

\*\*Values are recorded as means±SEM (n=5).

\*Values are statistically significant (p<0.05) in relation to control. One way ANOVA followed by Dunnett’post-hoc Multiple Comparison tests

**3.2 Motor Co-ordination Test**

The results indicated a significant reduction in the fall off time in rotarod test in haloperidol-treated group compared to the vehicle control group. However, this performance improved significantly with the administration of Bromocriptine at a dosage of 2.5 mg/kg, as well as MLEMP at doses of 200, 400 and 800 mg/kg. Table 2

TABLE 2: Effect MLEMP on motor coordination test using rotarod

|  |
| --- |
| Treatments Doses (mg/kg) Fall of Time (Sec)\*\* |
| Control 0 49.74±1.21  Haloperidol 1 14.32±1.17  MLEMP 200 50.17±2.05\*  MLEMP 400 59.12±0.51\*  MLEMP 800 67.45±0.19\*  Bromocriptine 2.5 61.43±1.81\* |

\*\*Values are recorded as means±SEM (n=5).

\*Values are statistically significant (p<0.05) in relation to control. One way ANOVA followed by Dunnett’post-hoc Multiple Comparison tests

**3.3 Effect of MLEMP on Locomotor Activity using actophotometer**

Table 3 showed a significant decrease in spontaneous motor activity in the group treated with haloperidol compared to the vehicle control group. However, the methanol extract of MLEMP significantly increased locomotor activity in a dose-dependent manner when compared to the animals treated with haloperidol.

*Table 3: Effect of MLEMP on Locomotor Activity using actophotometer*

|  |
| --- |
| Treatments Doses (mg/kg) Ambulations Counts/10 min\*\* |
| Control 0 161.3±6.15  Haloperidol 1 2.71±0.71  MLEMP 200 10.43±0.31\*  MLEMP 400 13.18±1.02\*  MLEMP 800 15.56±1.92\*  Bromocriptine 2.5 19.13±1.41\* |

\*\*Values are recorded as means±SEM (n=5).

\*Values are statistically significant (p<0.05) in relation to control. One way ANOVA followed by Dunnett’post-hoc Multiple Comparison tests

**3.4 Effect of MLEMP on haloperidol-induced Catalepsy in Mice**

Table 4 revealed that the haloperidol control group shows a significantly increased cataleptic score compared to the vehicle control group. MLEMP showed significant inhibition of catalepsy, decreasing the cataleptic score in a dose-dependent manner. Similarly, Bromocriptine also revealed a decrease in cataleptic score.

Table 4- Cataleptic scores

|  |
| --- |
| Treatments Doses (mg/kg) Cataleptic scores\*\* |
| Control 0 0  Haloperidol 1 2.78±0.12  MLEMP 200 1.98±0.17\*  MLEMP 400 1.21±0.05\*  MLEMP 800 0.75±0.07\*  Bromocriptine 2.5 0.73±0.01\* |

\*\*Values are recorded as means±SEM (n=5).

\*Values are statistically significant (p<0.05) in relation to control. One way ANOVA followed by Dunnett’post-hoc Multiple Comparison tests

**3.5 Effect of MLEMP MDA Levels**

**The brain MDA levels increases significantly (p<0.05) in the group treated with haloperidol compared to the control group. Conversely, the groups pretreated with MLEMP at 800 mg/kg and levodopa exhibited a significant decrease (p < 0.05) in brain MDA levels compared to the haloperidol-treated group, as shown in Table 5. Additionally, there was no significant difference in brain MDA levels between the groups treated with MLEMP at 800 mg/kg and those treated with levodopa.**

*Table 5: Effect of MLEMP on brain levels of MDA in haloperidol-treated mice.*

|  |
| --- |
| Treatments Doses (mg/kg) MDA(nmol/g tissue)\*\* |
| Control 0 194.1±5.23  HAL 1 602.6±9.21  MLEMP 200 597.3±7.30  MLEMP 400 591.7±7.45  MLEMP 800 235.5±6.33\*  Levodopa 30 230.3±6.17\* |

\*\*Values are recorded as means±SEM (n=5).

\*Values are statistically significant (p<0.05) in relation to control. One way ANOVA followed by Dunnett’post-hoc Multiple Comparison tests

**3.6 Effect of MLEMP GSH Levels**

**In the group treated with haloperidol, there was a significant decrease in brain glutathione (GSH) levels (p < 0.001) compared to the control group. However, the groups that received MLEMP at doses of 200, 400, and 800 mg/kg, as well as the levodopa-pretreated groups, showed a significant increase (p < 0.05) in brain GSH levels when compared to the haloperidol-treated group, as illustrated in Table 6. The group treated with levodopa showed a significantly greater effect compared to the group that received the extract.**

*Table 6: Effect of MLEMP on brain levels of GSH in haloperidol treated mice.*

|  |
| --- |
| Treatments Doses (mg/kg) GSH (μg/g tissue)\*\* |
| Control 0 547.8±9.03  HAL1 1 45.2±7.12  MLEMP 200 301.3±8.33\*  MLEMP 400 346.5±7.38\*  MLEMP 800 445.6±5.43\*  Levodopa 30 601.1±8.40\* |

\*\*Values are recorded as means±SEM (n=5).

\*Values are statistically significant (p<0.05) in relation to control. One way ANOVA followed by Dunnett’post-hoc Multiple Comparison tests

**4.0 DISCUSSION**

*“M. pruriens* is recognized as one of the plants that can counteract snake venom. Its seeds are commonly used in traditional medicine to mitigate the toxic effects of snake bites, which are primarily caused by potent toxins such as neurotoxins, cardiotoxins, cytotoxins, phospholipase A2 (PLA2), and proteases. The mechanisms behind the protective effects of the aqueous extract of *M. pruriens* seed have been reportedly studied” (Aguiyi and Cianti, 2008; Mukesh et al., 2017). “The plant was reported to contain a multiform glycoprotein, which stimulates the production of antibodies that cross-react with (bind to) certain venom proteins, an immunogenic component”(Aguiyi and Cianti, 2008; Mukesh et al.,2017).

“Parkinson’s disease is a chronic neurodegenerative disorder which may be due to the reduction in dopaminergic neurons present in the region of substantia nigra pars compacta. Several pathologies, including mitochondrial dysfunction, oxidative stress, protein accumulation such as alpha-synuclein, and apoptosis, are involved in this disease. However, the most important pathology of PD has been oxidative stress” (Friedlich et al., 2009). “Haloperidol-induced catalepsy, exploratory behaviour, the rotarod test, and locomotor activity are the most frequently used models for evaluating neurodegenerative disorders in animals. A specific complex I inhibitor (haloperidol) reproduces Parkinsonian signs and symptoms in rodents” (Chen et al., 2015; Rai et al,2017). “Many research studies have shown that systemic administration of haloperidol can lead to the degradation of dopaminergic neurons in the nigrostriatal pathway, which progresses the development of behavioural, neurochemical, and pathological events” (Chen et al., 2015). “The results of haloperidol-induced catalepsy showed that *Mucuna pruriens* provides a significant ameliorative effect on Parkinson’s disease in rats. The effect of *Mucuna pruriens* extract on rearing, muscle rigidity, and locomotor activity of rats was also evaluated, as earlier studies have shown that patients suffering from PD exhibit loss of brain motor coordination and are unable to maintain normal limb posture” (Bais et al., 2015). “Efficient locomotor activity was observed among the animals treated with *Mucuna pruriens* extract compared to the control group, providing further evidence of the ameliorative effect of *Mucuna pruriens* on PD. The assessment of oxidative stress biochemical parameters involved measuring brain MDA and reduced GSH levels. The group treated with Haloperidol showed a significant increase in brain MDA and a decrease in GSH levels. *Mucuna pruriens* and levodopa significantly decreased brain MDA levels and increased GSH levels. The biochemical test results of our study align with previous studies” (Polydoro et al., 2004). “The oxidative stress parameters, such as MDA and GSH, are positively influenced by *Mucuna pruriens*, which helps reduce oxidative damage to neurons. *Mucuna pruriens* is a medicinal plant of significant importance, playing a crucial role in protecting against oxidative stress. It has been suggested that antioxidants may protect neurons in Parkinson's disease by preventing degeneration caused by intracellular free radicals” (Slivka and Cohen, 1985).

“Inflammation and oxidative stress are widely recognized as interconnected. Oxidative stress can exacerbate inflammation, while inflammation can also lead to an increase in oxidative stress” (Teismann et al., 2003). “The role of neuroinflammation in Parkinson's disease (PD) has coincided with increasing interest in determining whether anti-inflammatory medications might help prevent PD. Recent studies have reported the role of inflammatory processes in the pathogenesis of Parkinson's disease (PD)” (Yuan et al., 2007).

“Experimental evidence from animal models supports a preventative role for non-steroidal anti-inflammatory drugs in Parkinson's disease” (Aubin et al., 1998).

**5.0 CONCLUSION**

The results of the present study conclusively showed that *Mucuna pruriens* has antioxidant activity and a neuroprotective role in the haloperidol experimental model of PD. *Mucuna pruriens* has been shown to improve rotarod performance and reduce catatonic responses. Therefore, the neuromodulatory effects of *Mucuna pruriens* on behaviour and oxidative stress may be attributed to its neuroprotective and antioxidant properties.

**DISCLAIMER (ARTIFICIAL INTELLIGENCE)**

Author(s) hereby declare that NO generative AI technologies such as Large Language Models

(ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

**CONSENT**

It’s not applicable.

**ETHICAL APPROVAL**

Animal Ethic committee approval has been collected and preserved by the author(s)

**COMPETING INTERESTS**

Authors have declared that no competing interests exist.

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