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Musa acuminata Colla Millsp ameliorates paraquat-induced memory deficit and oxidative stress in murine Parkinson disease model

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ABSTRACT

Background: Parkinson disease (PD) is one of the most common neurodegenerative disorders and remains an unmet medical need. A number of epidemiological as well as case-control studies have revealed an association between pesticide exposure, especially that of paraquat (PQ) and occurrence of PD. *Musa acuminata* Colla (Musaceae) also known as banana is widely cultivated for its delicious fruits and is one of the most economically important crops in the world. This study was designed to investigate the protective effect of *M. acuminata* fruit extract (MAC) on paraquat-induced Parkinsonism in mice.

Methods: Sixty male albino mice were randomly divided into 6 groups (n=10) and treated as follows for 21 consecutive days; Group 1: vehicle control (10 ml/kg, p.o.), group 2: vehicle + paraquat 10 mg/kg, i.p., group 3: MAC (400 mg/kg, p.o), groups 4-6: MAC (100, 200 or 400 mg/kg, p.o.) + paraquat, respectively. Behavioural studies (rotarod, Y-maze, open field test and bar test) were carried out on weekly basis. On day 21, one hour post-treatment the midbrains were isolated for biochemical estimation of oxidative stress parameters.

Results: MAC (100, 200 or 400 mg/kg) failed to reverse paraquat induced significant decrease in latency to fall in rotarod test. Similarly, MAC did not affect paraquat-induced decrease in locomotor activity in open field test. MAC prevented paraquat-induced decrease in percent alternation behaviour in Y-maze task. Conversely, MAC aggravated paraquat-induced cataleptic behaviour in bar test. The pretreatment of mice with MAC (200 or 400 mg/kg) significantly reversed paraquat-induced oxidative stress parameters in the midbrain.

Conclusion: Findings from this study showed that *M. acuminata* prevented paraquat-induced memory impairment through improvement in antioxidant defense mechanism but failed to reverse paraquat-induced locomotor deficit and cataleptic behaviour.

1. Introduction

Parkinson disease (PD) is one of the most common neurodegenerative disorder, affecting approximately 1% of individuals older than 60 years and causing progressive disability that can be slowed but not halted, by treatment[1]. The two major neuropathologic features of PD are loss of pigmented dopaminergic neurons of the substantia nigra pars compacta and the presence of Lewy bodies[2]. The main clinical features of PD are the tetrad of tremor at rest with a frequency of about 4Hz, postural instability, bradykinesia (a slowing of physical movement), muscle rigidity and in extreme cases akinesia (a loss of physical movement)[3,4].

PD etiology may be linked to several factors, including genetic susceptibility and environmental elements. Moreso, epidemiological studies have suggested that exposure to agricultural chemicals such as herbicide 1,1′-dimethyl-4,4′-bipyridium, paraquat (PQ), commonly used by farmers in developing countries may contribute to the pathogenesis of PD[5,6]. Moreover, several in vitro and in vivo PD-like models have been developed to understand the pathophysiology of PD and evaluate different therapeutic

strategies to fight dopaminergic neurodegeneration[7]. Paraquat belongs to the class of redox cycling compounds capable of inducing mitochondrial damage, increasing reactive oxygen species production and cellular stress[6].

Musa acuminata Colla (Mosaceae) is a species of banana native to Southeast Asia. Most of the modern edible dessert bananas belong to this species. All parts of the plant including fruits, peel, pseudostem, corm, flowers, leaves, sap and roots have found their use in the treatment of various diseases in traditional medicine[8]. Literature review have indicated use of *M. acuminata* in the treatment of various disease such as fever, cough, bronchitis, dysentery, allergic infections and some of the non-communicable diseases[8]. The reported pharmacological activities of *M. acuminata* include antioxidant, antidiabetic, immunomodulatory, hypolipidemic, anticancer and antimicrobial especially anti-HIV activity[8-10]. Moreso, M. acuminata is very rich in apigenin glycosides, myricetin glycoside, myricetin-3-O-rutinoside, naringenin glycosides, kaempferol-3-O-rutinoside, quercetin-3-O-rutinoside, dopamine, and N-acetylserotonin[11,12]. This study was carried out to evaluate the protective effect of *M. acuminata* peel extract on paraquat induced Parkinsonism in mice.

2. Materials and Methods

2.1 Materials

Paraquat (N'N'-dimethyl-4'-bipiridinium),thiobarbituric acid, sodium hydroxide, phosphate buffer saline, phosphoric acid, sulfanilamide, ethylenediame dihydrochloride, bovine serum albumin, trichloroacetic acid, potassium dichromate, 5,5-dithiobisnitro benzoic acid and glacial acetic acid were purchased from Sigma-Aldrich St. loius MO, USA.

2.2 Laboratory Animals

Sixty male albino mice (15-24g) were used in this study and randomly divided into 6 groups (n=10). They were obtained from the Laboratory Animal Centre of the College of Medicine, University of Lagos, Idi-araba, Lagos State, Nigeria. They were housed under standard laboratory condition maintained on a 12 hourly light-dark cycle with free access to food and water. Animals were acclimatized for a week to laboratory conditions before test. The experimental procedures adopted in this study was approved by the Health Research Ethics Committee of the College of Medicine, University of Lagos with approval number (CMUL/HREC/11/17/265) in accordance with the United States National Institutes of Health Guidelines for Care and Use of Laboratory Animals in Biomedical Research.

2.3 Plant material and preparation of extract

Ripe fruit of *M. acuminata* fruit was purchased from Ilasamaja fruit market, Lagos (6.5072° N, 3.3102° E). The fruit was washed and the peel removed and weighed. The peel (1.678kg) was blended with 750 mL of water giving a concentration of 2230 mg/ml. The stock was kept at 4°C.

2.4 Evaluation of acute toxic effect of *M. acuminata*

To evaluate the acute toxic effect of *M. acuminata,* twenty mice were randomly allotted to 4 groups; Group 1: vehicle (10 ml/kg, p.o.), Group 2: *M. acuminata* (100 mg/kg, i.p.), Group 3: *M. acuminata* (1000 mg/kg, i.p.) or Group 4: *M. acuminata* (5000 mg/kg, p.o.). The behavioural toxic effects (such as hyperactivity, hyperventilation, diarrhoea, urination and calmness) were observed for in the first 3 h and number of death recorded in 14 days.

2.5 Treatment regimen

Sixty male albino mice were divided into six groups (n=10) and treated for 21 consecutive days as follows:

Group 1: Vehicle (10 ml/kg, p.o. normal control), group 2: MAC (400 mg/kg, p.o.), group 3: vehicle (10mg/kg, i.p negative control), group 4-6: MAC (100, 200 or 400 mg/kg, p.o.). Animals in group 3-6 were exposed to paraquat (10 mg/kg, i.p) twice a week for 3 weeks.

The spontaneous motor activity was assessed during the 21 days using the open field test (locomotor activity), rotarod performance (motor coordination), bar tests (catalepsy) and Y-maze test (working memory). The animals were sacrificed on day 21 for biochemical markers of oxidative and nitrosative stress.

2.6 Rotarod Performance Test for motor coordination

The rotarod performance test is used to assess motor co-ordination[13]. The animals were placed on the horizontally oriented rotating cylinder (rod) suspended above a cage floor, which is low enough not to injure the animal, but high enough to induce avoidance of fall. Animals were trained before the test and animals which stayed on the rotarod for 120 seconds were used for this study. The animals were subjected to rotarod test on days 2 and 11. Time of falling was recorded[13].

2.7 Open Field Test for locomotor activity

The open field test provides simultaneous measures of locomotion, exploration and anxiety[14]. The number of line

crosses and the frequency of rearing were used as measures of locomotor activity[14]. The animals were allowed to acclimatize to laboratory environment 1 h before the study. One hour post treatment the number of crosses was recorded for 2 min after 1 min of acclimatization on days 2 and 8.

2.8 Y-maze test for working memory

The Y-maze is used to assess short term memory, general locomotor activity and stereotypic behaviour[15]. Spontaneous alternation was assessed using Y- maze comprising of three equally spaced arms labelled A, B, C (120°, 41 cm long and 15 cm high). Each mouse was placed in one of the arm compartment and allowed to move freely until its tail completely enters another arm. The sequence of arm entries were manually recorded on days 4 and 18. The percentage alternation behaviour (visitation of three different arms ABC, BAC, CAB, BCA, CBA etc = alternation)[15] in 5 minutes.

2.9 Bar test for catalepsy

The standard bar test is used to determine the intensity of catalepsy[16]. Both fore legs of the mice were placed on a horizontal bar (diameter, 0.7cm) 9 cm above the surface. Treatment was carried out on days 6 and 13. The animals were placed on the bar for 60s and the latency time of removal of paw of each animal was observed and recorded.

2.10 Brain tissue preparation and estimation of oxidative stress markers

The mice were decapitated under chloral hydrate (300 mg/kg, i.p.). The skull was cut open and the brain was exposed from the dorsal side. The whole brain was quickly removed and the mid brain was isolated and cleaned with chilled normal saline on ice, blotted and weighed. A 10% (w/v) homogenate of brain sample (0.1M phosphate buffer, pH: 7.2) was prepared by using mortar and pestle. The resulting homogenate was centrifuged at 2000rpm speed for 15mins then it was removed from the centrifuge and the supernatant was decanted and stored at -20°C until analysis[13]. The earlier established and reported protocols were used to measure lipid peroxidation (malondialdehyde (MDA))[17], nitrite[18], superoxide dismutase (SOD)[19], glutathione (GSH)[19] and catalase[19].

2.11 Statistical Analysis

Data are expressed as mean ± SEM and analyzed using one or two way analysis of variance (ANOVA) followed by Tukey's *post hoc* multiple comparison test.

3. Results

3.1 Rotarod Performance Test

Intraperitoneal administration of paraquat did not affect motor coordination up to day 11 but MAC 200 or 400 mg/kg + paraquat treated caused significant decrease in motor coordination. Post hoc analysis revealed significant decrease in falling time in paraquat treated mice from day 11 when compared with vehicle treated control. MAC (100-400 mg/kg) failed to reverse paraquat-induced motor coordination deficit. Interestingly, MAC 400mg/kg only did affect motor coordination (Fig. 1)

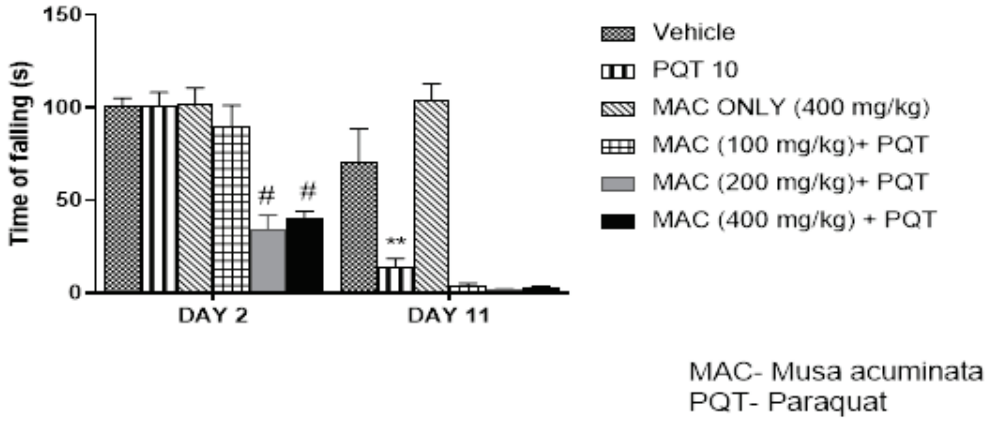
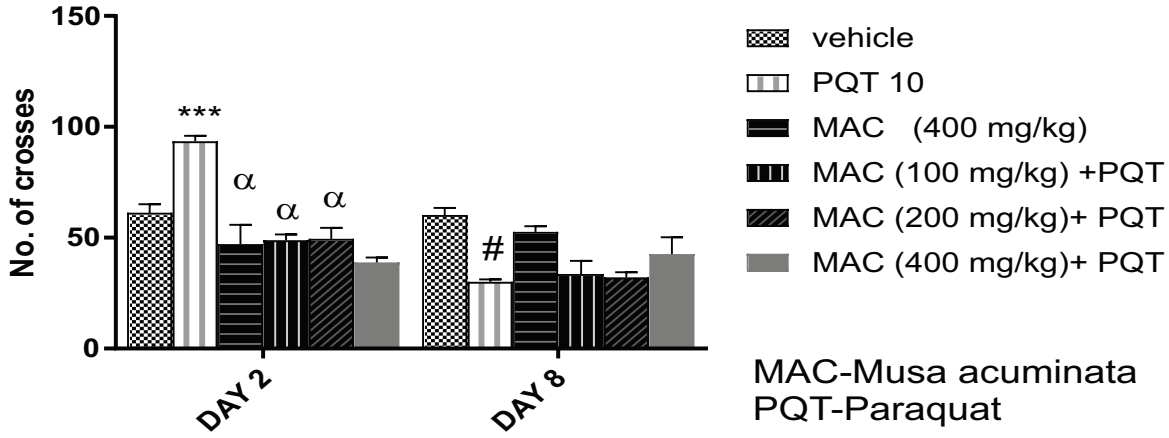


Figure 1: Effect of *M. acuminata* on motor coordination in rotarod test. Values were presented as mean ± SEM (n=6). P<0.05 versus vehicle control; p<0,05 versus paraquat-vehicle treated. Statistical analysis by two way ANOVA followed by Tukey's *post hoc* multiple comparison test.

3.2 MAC failed to reverse paraquat-induced locomotor deficit in open field test

Exposure of mice to paraquat caused significant increase in number of line crosses in the first two days of administration compared to vehicle control (Figure 2). Conversely MAC 100-400 mg/kg treated caused no significant change when compared to normal control but reduced number of crosses when compared with paraquat treated group. By day 8, paraquat caused significant decrease in number of crosses when compared with vehicle treated control. MAC produced no significant effect at the 8th day when compared with paraquat treated group (Fig. 2).

Figure 2: Effect of *M. acuminata* on locomotor activity in open field test. Values were presented



as mean ± SEM (n=6). ***P<0.001 versus vehicle control; #P<0.05 versus vehicle control; αp<0.05 versus paraquat-vehicle control. Statistical analysis by two-way ANOVA followed by Tukey's *post hoc* multiple comparison test.

3.3 MAC reversed paraquat-induced working memory in Y-maze test

Paraquat exposure caused significant decrease in percent spontaneous alternation behaviour from day 4 when compared with vehicle treated group. However, paraquat-induced alternation deficit was significant reduced by MAC (100-400 mg/kg) (Figure 3).

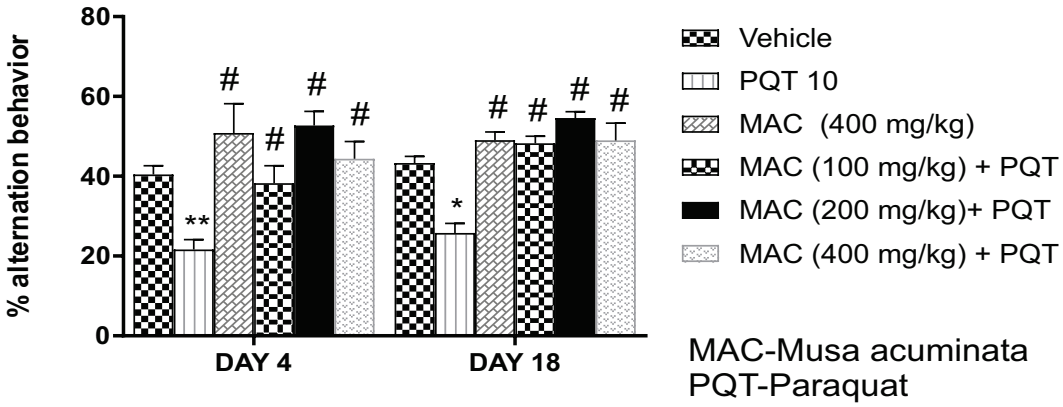


Figure 3: Effect of *M. acuminata* in Y-maze test. Values were presented as mean± SEM (n=6). *P<0.001 versus vehicle control; **p<0.01 versus vehicle control; #P<0.05 versus paraquat-vehicle control. Statistical analysis by two-way ANOVA followed by Tukey's *post hoc* multiple comparison test.

1.4. MAC aggravated paraquat-induced catalepsy in bar test

Paraquat induced significant cataleptic behaviour by day 13 when compared with vehicle treated control. Similarly, paraquat-induced cataleptic behaviour was significantly aggravated by MAC (100-400 mg/kg) when compared with paraquat-vehicle treated (Fig. 4).

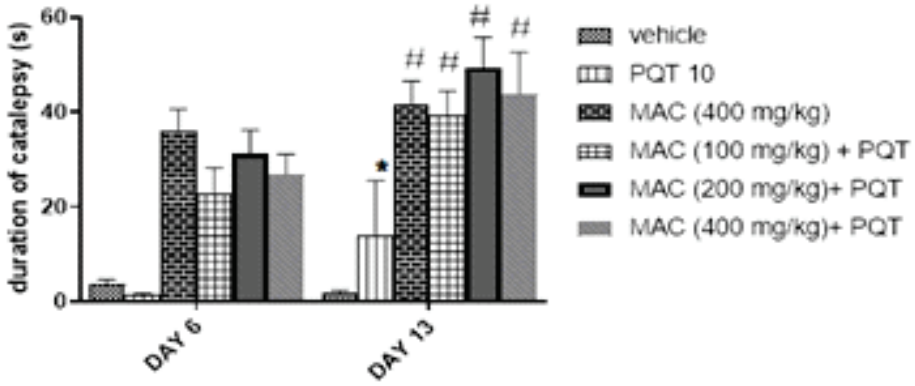


Figure 4: Effect of *M. acuminata* in bar catalepsy. Values were presented as mean ± SEM (n=6). *p<0.05 versus vehicle treated control; #p<0.05 versus paraquat-vehicle treated control. Statistical analysis by two-way analysis of variance (ANOVA) followed by Tukey's *post hoc* multiple comparison test.

3.5 MAC attenuates oxidative stress parameters in the midbrain

Paraquat subchronic exposure caused significant generation of nitrite in the midbrain when compared with vehicle treated (Fig.5a). MAC failed to attenuate paraquat-induced nitrite generation when compared with paraquat-vehicle treated. Paraquat caused significant elevation of MDA when compared with vehicle control. MAC (100-400 mg/kg) produced significant decrease in MDA level compared with paraquat-vehicle control (Fig. 5b). MAC (100-400 mg/kg) caused significant increase in GSH level when compared with paraquat-vehicle treated control (Fig. 5c). Conversely, both MAC and paraquat administration did not affect superoxide dismutase activity in the brain (Fig. 5d).

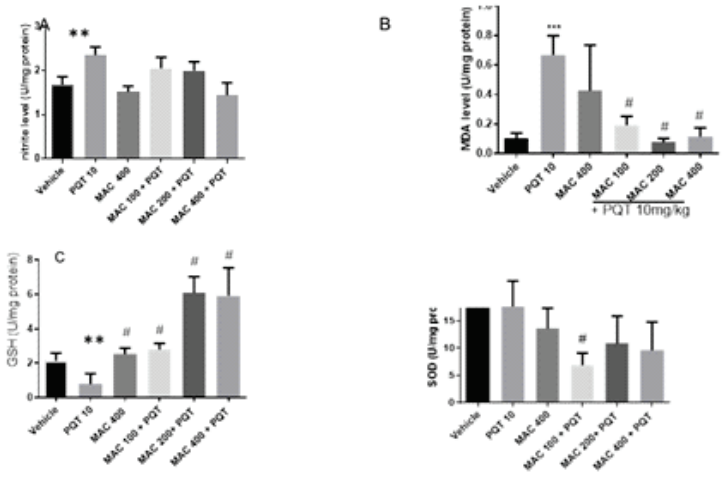


Figure 5a-d: Effect of *M. acuminata* and paraquat treatments on (a) nitrite level, (b) malondialdehyde level, (c) glutathione level and (d) superoxide dismutase activity in mice brains. Values were presented as mean ± SEM (n=6). **p<0.01; p<0.001 versus vehicle treated control; #p<0.05 versus paraquat-vehicle treated control. Statistical analysis by one way analysis of variance (ANOVA) followed by Tukey's *post hoc* multiple comparison test.

4. Discussion

Epidemiological studies have suggested that exposure to agricultural chemicals is associated with an increased risk of developing PD[2]. Pesticides/herbicides, such as paraquat causes neurotoxicity and induce a PD-like pathology. Interestingly, findings from this study showed that paraquat reduces falling time, locomotor activity and spontaneous alternation behaviour in rotarod, open field and Y-maze tests, respectively, suggestive of neurotoxicity and cognitive deficit. Moreover, paraquat produced cataleptic behaviour in bar test as well as induction of oxidative stress indicative of Parkinsonism. However, paraquat-induced cognitive deficit and oxidative stress were ameliorated by M. acuminata indicative of memory enhancing and antioxidant activities but aggravate paraquat-induced catalepsy without affecting spontaneous motor and locomotor activities.

To assess the neuroprotective action of *M. acuminata*, its effect on balance and gait performance was assessed in rotarod test. Loss of gait performance and balance has been associated with unilateral degeneration of dopamine neurons in the substantia nigra[15,20]. In this study, intraperitoneal injection of paraquat reduced balance and gait performance indicative of neurotoxicity[15]. However, pretreatment of mice with *M. acuminata* failed to reverse paraquat induced motor deficit in rotarod test.

Similarly, open field test was carried out to assess effect of treatments on locomotor activity[20]. Interestingly, paraquat reduced locomotor activity suggestive of Parkinsonism but oral administration of *M. acuminata* failed to reverse paraquat induced motor deficit in open field test.

Catalepsy bar tests are widely used to measure the failure to correct an imposed posture resulting from muscular rigidity. Studies have shown that catalepsy is related to decreased dopamine (DA) transmission at postsynaptic D_2 receptors[21]. In agreement with previous studies paraquat induced cataleptic behaviour[15,20]. Moreover, paraquat induced cataleptic behaviour was aggravated by *M.acuminata* administration possibly due to its richness in dopamine[8]. Moreover, catalepsy and the selective suppression of conditioned avoidance response are often used as animal models to predict extrapyramidal side effect[21].

Y-maze task detect the lateralization of hemiparkinsonian animals in terms of biased turns in the maze as well as working memory function[13,22]. In this study, exposure of mice to paraquat reduced spontaneous alternations behaviour indicative of working memory deficits in agreement with previous studies[13,16]. However, the pretreatment of mice with *M. acuminata* reversed the decrease in spontaneous alternation behavior suggestive working memory improvement.

Mitochondrial dysfunction and oxidative stress are pathophysiologic mechanisms implicated in experimental models and genetic forms of PD[23]. Disruptions in the physiologic maintenance of the redox potential in neurons interfere with several biological processes, ultimately leading to cell death[9]. The body fights against ill effects of free radicals via antioxidant defense system comprising of antioxidant enzymes like SOD, GSH etc. Paraquat belongs to the class of redox cycling compounds capable of inducing mitochondrial damage, increasing reactive oxygen species production and oxidative stress through inhibition of mitochondrial complex I transport chain[3]. The imbalance between increased production of free radicals and decreased antioxidant capacity, results in a persistent lipid peroxidation. In this study, paraquat increased the level of malondialdehyde suggestive of lipid peroxidation which was attenuated by the pretreatment of mice with *M. acuminata* possibly due its richness in neuroactive flavonoids such as apigenin glycosides, myricetin glycoside, myricetin-3-O-rutinoside, naringenin glycosides, kaempferol-3-O-rutinoside, quercetin-3-O-rutinoside, dopamine, and N-acetylserotonin[11,12]. Similarly, paraquat caused an increase in nitrite generation which was attenuated by *M. acuminata* further supporting its antioxidant activity. GSH is the prominent endogenous antioxidant in mammalian cells and its homeostasis relies on activity of a number of antioxidant enzymes such as catalase and SOD[6]. In this study, paraquat caused a decrease in glutathione level which was reversed by *M. acuminata* further affirming its antioxidant defense capability against neurotoxin.

5. Conclusion

The behavioural studies showed that the administration of paraquat induced motor and memory deficit in mice. Paradoxically, *M. acuminata*-paraquat co-exposure restored memory impairment but not the motor deficits possibly through enhancement of antioxidant defense signaling.

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Conflict of interest

We do not have any conflicting interest to declare

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