



Neuroprotective Effects of *Garcinia kola* ethanol Seed Extract on Haloperidol-Induced Catalepsy in Mice

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ARTICLE INFO

Article history:

Received 06 February 2022

Revised 23 February 2022

Accepted 01 March 2022

Published online 06 March 2022

ABSTRACT

Antipsychotic drugs are known to cause irreversible neurodegeneration through oxidative mechanisms. *Garcinia kola* is known for its capacity to scavenge free radicals. This study elucidated the neuroprotective properties of ethanol extract of *Garcinia kola* (EGK) nuts on haloperidol (HP)-induced catalepsy. Forty male Swiss albino mice (*Mus musculus*) (2-3 weeks old, 19-25g) were grouped into 8 (n=5) as follows: Groups I (2 mL/kg propylene glycol), II (haloperidol(HP)), III (200 mg/kg + HP) and IV (400 mg/kg EGK + HP), V(HP + 200 mg/kg EGK), VI (HP + 400 mg/kg EGK), VII (HP + 200 mg/kg EGK) and VIII (HP + 400 mg/kg EGK). Haloperidol was administered intraperitoneally at a dose of (1 mg/kg). Neurobehavioural assessments for locomotor activity, memory, anxiety and catalepsy scoring involved the use of elevated plus maze and the open field apparatus on the 1st, 8th, and 15th day of the study. Brain malondialdehyde (MDA) and glutathione (GSH) concentrations were assayed using colorimetric method. Haloperidol significantly reduced (p<0.05) body weight, impaired motor coordination, memory, locomotor and also promoted anxiety as well as lipid peroxidation. However, treatment with EGK significantly (p<0.05) reversed weight loss, improved locomotor activity and memory function, curtailed anxiety and brain lipid peroxidation. EGK conferred neuroprotection and can be suggested for possible use in the management of haloperidol-induced neurodegeneration.

Keywords: *Garcinia kola*, Haloperidol, Catalepsy, Neurodegeneration, Lipid peroxidation.

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Introduction

Catalepsy is a manifestation of many neurological disorders such as schizophrenia, psychosis, epilepsy, catatonia, Parkinson's disease as well as the typical manifestation of withdrawal from chronic cocaine consumption.¹ It is a neurological disorder characterized by motor coordination problems, such as muscle twitching, as well as autonomic irregularities, such as decreased breathing rate.²

Catalepsy is also a classic devastating contraindication to traditional antipsychotic medications such as haloperidol.³ Haloperidol is a broad-spectrum antipsychotic medicine used to treat schizophrenia, bipolar disorder mania, acute psychosis, alcohol withdrawal and hallucinations etc.⁴ However, cumulative dose-dependent adverse effects typically limit its pharmacological significance.⁵ In Parkinson's disease, haloperidol reduces the efficiency of levodopa by inhibiting dopamine D₂ receptors in the corpus striatum, resulting in reduced dopaminergic transmission.⁶ This could result in a loss of motor function, a return of psychosis, or a combination of the two.

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Citation: David AA, Oladele AA, Philip AO, Zabdiel AA, Olufunso AB, Tolulope OO, Adebola AO. Neuroprotective Effects of *Garcinia kola* ethanol seed Extract on Haloperidol-Induced Catalepsy in Mice. Trop J Nat Prod Res. 2022; 6(2):281-286. doi.org/10.26538/tjnpr/v6i2.18

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

Unfortunately, there is presently no effective conventional drug to counteract the effects of haloperidol-induced neurotoxicity. The development of natural supplements as adjuvants is unavoidable in order to improve treatment outcomes while reducing related life-threatening contraindications. *Garcinia kola* is known as a miracle plant in traditional medicine due to the numerous medicinal effects of the various plant parts. The plant is known as bitter kola in traditional and complementary medicine because of its aphrodisiac properties.⁷ Yoruba, Igbo, and Hausa ethnic groups in Nigeria refer to *Garcinia kola* as Orogbo, Aku ilu, and Namijin Goro, respectively.⁸ *Garcinia kola* seed is offered to guests in various societies, especially at traditional social occasions. Its antioxidative activity is always linked to its effect in alleviating pathogenic symptoms.^{9,10} *Garcinia kola* seeds are rich in vital nutrients such as carbohydrate, proteins, minerals, and vitamins.¹¹ The unique biflavonoid composition of *Garcinia kola* seed extract, known as kolaviron, is frequently credited with the underlying free radical scavenging action.¹² While the chemotherapeutic effects of various *Garcinia kola* seed extracts have been established in multiple organs using various animal models, the neuroprotective properties of its ethanolic seed extract in mitigating haloperidol-induced catalepsy have sadly not been investigated. The neuroprotective potential of *Garcinia kola* seed extracts in haloperidol-induced catalepsy were investigated in the present study.

Materials and Methods

Garcinia kola

Garcinia kola nuts were obtained from the Mayfair market in Ile-Ife and identified at Obafemi Awolowo University's Department of

Botany in Ile-Ife in February, 2018. The voucher number (IFE-17625) was received after a specimen was placed to the herbarium for future reference.

Chemical reagents

Haloperidol was obtained from Jansen Pharmaceutical Company, Beerse, Belgium. Ethanol, propylene glycol, and other reagents were purchased at the British Drug House (BDH) (Poole, England). Other analytical grade chemicals were procured at either BDH or Sigma – Aldrich (MO, USA).

Extraction of *Garcinia kola*

The nuts were split into little pieces, weighed, and dried in the shade for three weeks. Using a Warring blender, the air-dried particles were crushed to powder and weighed. Approximately 4100 g of powder was macerated for three days in 10 liters of ethanol, with frequent shaking with an electric shaker. After that, the mixture was filtered through Whatman No. 1 filter paper. The filtrate was then weighed and freeze-dried in a lyophilizer after being evaporated at reduced pressure with a rotary evaporator. The extracted substance was then kept at 40°C. The percentage yield of the extract was determined with the formula:

$$\frac{\text{dry extract weight}}{\text{dry material weight}} \times 100\%$$

Preparation of Stock Solution For Ethanol Extract of *Garcinia kola* (EGK)

To make the extract stock solution, 2 g and 4 g of *Garcinia kola* ethanol extract were poured into separate sterile specimen bottles. Afterwards, 10 mLs of propylene glycol were added to the two specimen bottles containing the extract to make concentrations of 200 mg/mL and 400 mg/mL, respectively. Each three days, a new solution was created after the final solution had been vigorously shaken. An oral cannula fitted with a syringe was used to administer an ethanol extract of *Garcinia kola* (EGK) orogastrically.

Preparation of stock solution for haloperidol

In a sterile universal bottle, 5 mg of haloperidol was added to 10 mL of normal saline, resulting in a concentration of 0.5 mg/ml. The solution was shaken violently every day, and a new solution was created every day. To induce catalepsy, 1 mg/kg haloperidol (HP) was injected intraperitoneally using an insulin syringe.

Animal Use and Care

Forty (40) mice (*Mus musculus*) (17g-22g) were obtained from Obafemi Awolowo University, Ile-animal Ife's holding unit and housed in well-ventilated mice cages for two weeks to acclimate to a 12-hour day/night cycle. Unlimited access to clean drinking water and standard chow were given. All mice were treated humanely in accordance with standard protocols.

Experimental design

Mice were randomly grouped into eight (n = 5). A dose of 1 mg/kg of haloperidol was chosen based on previous report.¹³ The bodyweight of mice in each group was measured weekly using a digital weighing balance. The mice grouping, dose regimen, and administration schedule were as follows;

Neurobehavioural assessment

On the last day 14 (final day of the experiment), neurobehavioural parameters such as anxiety and locomotor activity were evaluated. The open field test and elevated plus maze apparatus were used.¹⁴ For acclimatization, mice in each group were placed in the behavioural testing room for at least 1 hour before the test period.

Catalepsy scoring

The catalepsy score was estimated using a previously described method.¹⁵ Each mouse was carefully placed in the center square of the open field device. Only once the animal was completely immobile, with no head or limb movement, was catalepsy considered. During a

two-minute observation period, the length of the longest immobility episode was utilized to estimate the severity of the cataleptic state. If the animal was still immobile after two minutes, it was observed until it made its first movement; normally, the immobility period ends with a head movement. This process was performed for each animal to determine the average immobility time. A stopwatch was used to record the longest time the animal stayed completely immobile. The animal's longest period of total immobility was measured in minutes using a stopwatch with a precision of 0.2 seconds.

Open field test

Each mouse was placed in the center of the contraption and given 5 minutes to explore it. To avoid olfactory cues, mice were returned to their home cages after the 5-minute testing session, and the open field was wiped off with 70% ethyl alcohol and left to dry between tests. Each mouse was given fifteen minutes of exposure to the apparatus device before being timed. Line crossing, rearing frequency, and immobility time were all rated as behavioural outcomes. The sum of the lines traversed and the number of rears was then used to compute each rat's overall locomotor activity.

Elevated plus maze

The equipment was raised 45 cm above the floor on a plus-shaped plywood foundation. Mice were brought into the test room in their home cages and handled by the base of their tails at all times. Mice were placed in the Plus-central Maze's square, facing an open arm, and given 5 minutes to explore the device. An unidentified observer sat discreetly about a meter away from the apparatus, recording the animals' behaviour through the maze. After 5 minutes, the mice were recovered from the maze by the base of their tails and returned to their home cage. Between experiments, the maze was cleaned with a 70% ethyl alcohol solution and left to dry. Open arms entrances and closed arms entries were among the behavioural outcomes assessed.

Animal sacrifice

A day following the last medication delivery, mice from each group were weighed and sacrificed via cervical dislocation. Using bone forceps, the mice's skulls were meticulously dissected, and the brain tissues were removed, weighed, and stored at -20° C until needed for biochemical analysis.

Determination of body weight change (BWC)

The percentage body weight change (BWC) was calculated by:

$$BWC = \frac{\text{final weight} - \text{initial weight}}{\text{Initial weight}} \times 100\%$$

Determination of relative brain weight (RBW)

The relative brain weight (RBW) was estimated by:

$$RBW = \frac{\text{brain weight}}{\text{Final body weight}} \times 100\%$$

Biochemical assay procedure

After allowing whole-brain tissues to thaw, they were homogenized in four liters of ice-cold 0.1M phosphate buffer. A supernatant solution was obtained by centrifuging the resulting mixture at 4000 rpm. A biochemical experiment was performed using the supernatant solution.

Determination of malondialdehyde,

Malondialdehyde concentration in the brain tissue was analyzed as previously described by¹⁶. In the reaction mixture, 0.5 mL plasma sample, 0.5 mL phosphate buffer (0.1 M, pH 8.0), and 0.5 mL 24 percent TCA were combined. The resulting mixture was incubated for 10 minutes at room temperature before being centrifuged for 20 minutes at 2000 rpm. To 1 mL of supernatant, 0.25 mL of 0.33 percent TBA in 20 percent acetic acid was added, and the mixture was incubated at 95°C for 1 hour. After chilling the pink-colored product, absorbance was measured at 532 nm.

Estimation of reduced glutathione (GSH)

Reduced glutathione (GSH) was measured by the method of Ellman. 1 mL of the supernatant from the centrifuge tube was taken, 0.5 mL of Ellman's reagent (10mM) and 2 mL of phosphate buffer (0.2 M, pH 8.0) were added. Using a blank containing 3.5 mL of phosphate buffer, the produced yellow hue was detected at 412 nm. GSH concentrations were calculated in milligrams per 100 grams of brain tissue.

Statistical analysis

On Graph Pad 5.03, data were analyzed using one-way analysis of variance (ANOVA), and post-hoc analysis was performed using the Student Neuman-Keuls test (Graph Pad Software Inc., CA, USA). P values less than 0.05 were deemed significant. All data were reported as mean standard error of the mean (SEM).

Results and Discussion

Over time, neuroleptic or antipsychotic drugs like haloperidol have been used in animal models of cataleptic behaviour. Haloperidol-induced catalepsy is defined as a lack of reactivity to external stimuli, as well as muscle rigidity or animals' inability to adjust an externally imposed position.¹ The potential neuroprotective effects of *Garcinia kola* seed extract on haloperidol-induced catalepsy in mice were investigated using neurobehavioural and biochemical techniques. *Garcinia kola* seed ethanolic extraction provided a final weight of 296.6 g, resulting to a percentage yield of 7.23%. Haloperidol treatment significantly reduced ($p < 0.05$) locomotor activity in the negative control (1 mg/kg HP) group in comparison with the vehicle control (2 mL/kg propylene glycol) group. Interestingly, pretreatment with an ethanol extract of *Garcinia kola* (200 mg/kg EGK + HP; 400 mg/kg EGK + HP) significantly ($p < 0.05$) reduced the effects of haloperidol on locomotor performance. This therapeutic action suggests that certain bioactive compounds in *Garcinia kola* ethanol extract interact with dopamine metabolism metabolic pathways. When compared to the normal control group, the number of entry into the enclosed arms of the plus-maze apparatus increased significantly ($F = 4.972$, $p = 0.0171$). This is suggestive of haloperidol induced anxiety. Similar observation has been documented by previous investigators.²² Supplementation with ethanol extract of *Garcinia kola* reduced the anxiety-like effects of haloperidol in the pretreatment groups (200 mg/kg EGK + HP; 400 mg/kg EGK + HP), concomitant groups (HP + 200 mg/kg EGK; HP + 400 mg/kg EGK), and treatment groups (HP + 200 mg/kg EGK; HP + 400 mg/kg EGK). The pretreatment and concomitant groups, on the other hand, experienced a considerable reduction in immobility time. The relative improvement in immobility produced by *Garcinia kola* ethanol extract may be a result of its component kolaviron, a neuroprotective chemical.²³ This improvement is likely to be due to EGK's antioxidant action against haloperidol-induced oxyradical assaults on dopaminergic neurons. When compared to the normal control, the total time spent in the closed arms of the elevated plus-maze was significantly increased ($p < 0.05$) in haloperidol treated mice. Following treatment of ethanolic extract of *Garcinia kola*, animals in the pretreatment groups (200 mg/kg EGK + HP; 400 mg/kg EGK + HP) demonstrated a significant, dose-dependent reduction in total time spent in the closed arms of the elevated plus maze. Also, the total time spent in the closed arms of the elevated plus maze was significantly reduced in the concomitant (HP + 200 mg/kg EGK; HP + 400 mg/kg EGK) and treatment groups (HP + 200 mg/kg EGK; HP + 400 mg/kg EGK) groups compared to the vehicle control (2 mL/kg propylene glycol) and haloperidol only (1 mg/kg) groups. Furthermore, pretreatment of mice with *Garcinia kola* extracts in groups III (200 mg/kg) and IV (400 mg/kg) with ethanol extract of *Garcinia kola* decreased depressive-like behaviour, immobility, and anxiety. This suggests that pretreatment of extract may have likely increased the brain's antioxidant defense mechanisms, resulting in improved physiological state. When compared to mice in the vehicle control (2 mL/kg propylene glycol) group, the number of lines crossed in the open field apparatus was significantly reduced ($p < 0.05$) in haloperidol (1mg/kg) only mice (Figure 3).

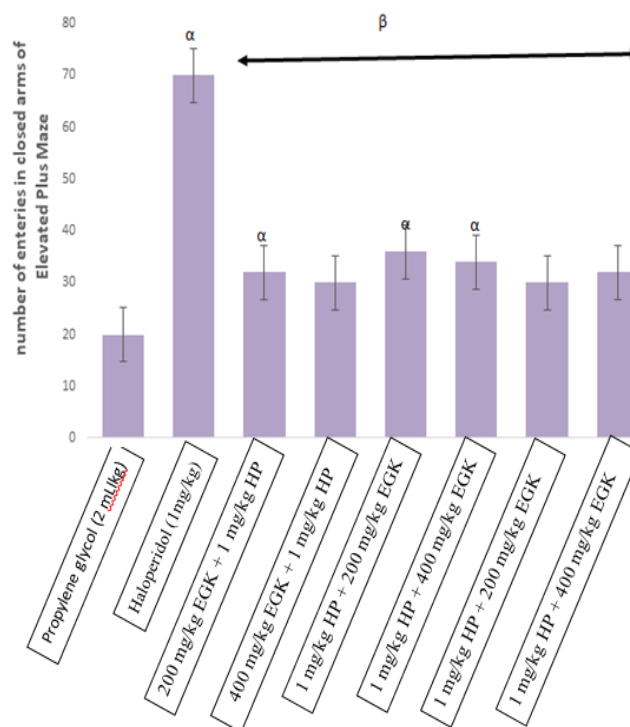


Figure 1: Effect of ethanol extract of *Garcinia kola* on the number of entries into the closed arms of elevated plus-maze apparatus following Haloperidol administration. Results are presented as Mean ± SEM, n=5; α = significantly different from control ($p < 0.05$); β = significantly different from group II ($p < 0.05$).

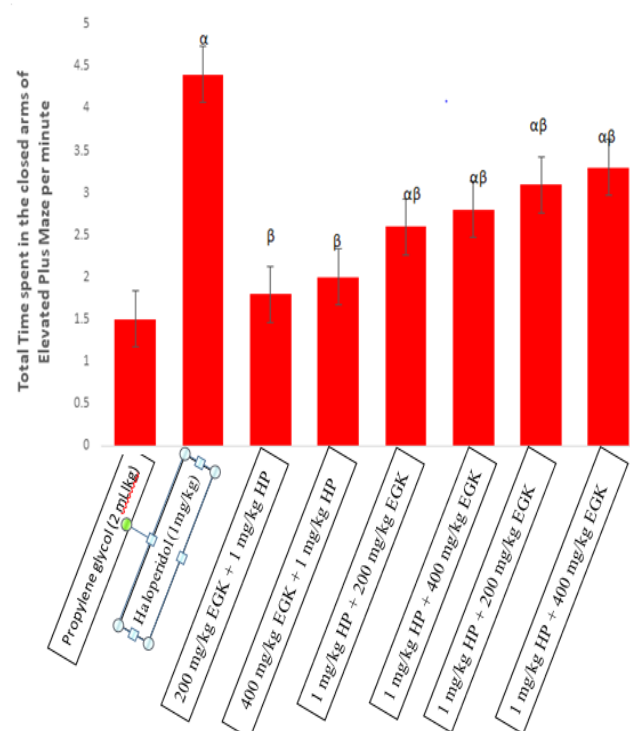


Figure 2: Effect of ethanol extract of *Garcinia kola* on the total time spent in the closed arms of elevated plus-maze apparatus following Haloperidol administration. Results are presented as Mean ± SEM, n=5; α = significantly different from control ($p < 0.05$); β = significantly different from group II ($p < 0.05$).

In a dose-dependent manner, pretreatment of mice in groups III (200 mg/kg EGK + HP) and IV (400 mg/kg EGK + HP) increased the number of lines crossed in open field apparatus compared to vehicle control (2 mL/kg propylene glycol) and haloperidol (1 mg/kg) only groups. However, compared to vehicle control (2 mL/kg propylene glycol) and haloperidol (1 mg/kg) only mice, there was a significant increase in the number of lines crossed in open field apparatus across the concomitant groups (HP + 200 mg/kg EGK; HP + 400 mg/kg EGK) and treatment groups (HP + 200 mg/kg EGK; HP + 400 mg/kg EGK) in a dose-dependent manner. Furthermore, when compared to the propylene glycol (2 mL/kg) group, haloperidol administration resulted in a significant reduction in bodyweight ($P = 0.0346$, $F = 2.66$) in the haloperidol alone (1 mg/kg) experimental animals. This finding is consistent with that of a previous investigator.¹⁷ By producing masticatory muscle stiffness and, as a result, difficulties eating, haloperidol medication may have predisposed to significant weight loss. Aside from antipsychotics' transient antagonistic effects on D_2 receptors, haloperidol can also function as a selective antagonist of specific brain receptors involved in body weight regulation.¹⁸ The antagonistic effects of haloperidol on relevant receptors in the central nervous system may therefore be responsible for the downstream biochemical cascades that evoked considerable weight loss. Pretreatment with an ethanol extract of *Garcinia kola*, on the other hand, prevented considerable weight reduction. The phytochemical constituents of *Garcinia kola* ethanol extract, which contain proteins, vitamins, carbohydrates, and mineral components, may be responsible for this pharmacological activity. Significant weight reduction was found in both the concurrent and therapy groups, however. This is most likely due to hydroxy citric acid (HCA), a bioactive compound found in *Garcinia kola* which is reputed for lowering body fat¹⁹ and consequently, body weight.²⁰ HCA is a competitive inhibitor of the extramitochondrial enzyme ATP-citrate-lyase, which inhibits lipogenesis, resulting in weight loss and appetite suppression.²¹ As a result, the significant weight loss in the experimental groups could be attributed to the combined effects of haloperidol and HCA. Figure 6 shows that haloperidol administration resulted in a non-significant ($p > 0.05$) reduction in relative brain weight when compared to control, but there was no significant difference in relative brain weight when ethanol extract of *Garcinia kola* treated groups were compared. Following haloperidol treatment, the malondialdehyde (MDA) levels of group II (1 mg/kg HP) mice increased significantly ($p < 0.05$) when compared to group I (2 mL/kg propylene glycol) (Figure 7). Furthermore, when compared to haloperidol (1 mg/kg HP) only group, MDA levels were significantly lower ($p < 0.05$) in the pretreatment groups (200 mg/kg EGK + HP; 400 mg/kg EGK + HP), concomitant groups (HP + 200 mg/kg EGK; HP + 400 mg/kg EGK), as well as the treatment groups (HP + 200 mg/kg EGK; HP + 400 mg/kg EGK). Meanwhile, there was also a significant decrease ($p = 0.02103$, $F = 1.9753$) in the GSH levels of group II (1mg/kg HP) relative to group I (2 mL/kg propylene glycol). These observations are consistent with those of a prior study.²² These findings suggest that haloperidol administration increased lipid peroxidation in brain tissues, potentially leading to a severe metabolic state known as haloperidol-induced oxidative stress. Increased dopamine turnover via monoamine oxidase, which boosts hydrogen peroxide levels, has been associated to haloperidol-induced oxidative stress in brain cells.²³ Treatment with *Garcinia kola* seed extract significantly reduced haloperidol-induced oxidative stress, as evidenced by a significant decrease ($p < 0.05$) in MDA and a consequent rise in GSH. *Garcinia kola*'s antioxidant effect is thought to be due to the termination of chain reactions in lipid peroxidation.²⁴ Although *Garcinia kola* is well-known for being a rich source of vital phytochemicals with powerful antioxidant qualities. Some of its bioactive components may be able to penetrate the blood-brain barrier, providing neuroprotection. Kolaviron, garcinal, and garcinoic acid are a few examples.²⁵ Thus, therapeutic effects of *Garcinia kola* against haloperidol-induced lipid peroxidation may have been elicited by its functional bioactive mechanisms.

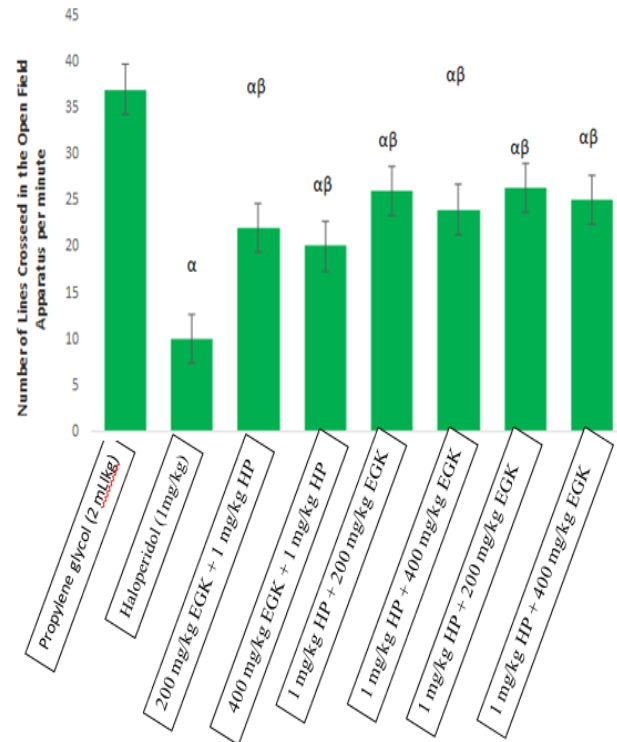


Figure 3: Effect of ethanol extract of *Garcinia kola* on the number of lines crossed in open field apparatus following Haloperidol administration. Results are presented as Mean \pm SEM, $n=5$; α = significantly different from control ($p < 0.05$); β = significantly different from group II ($p < 0.05$).

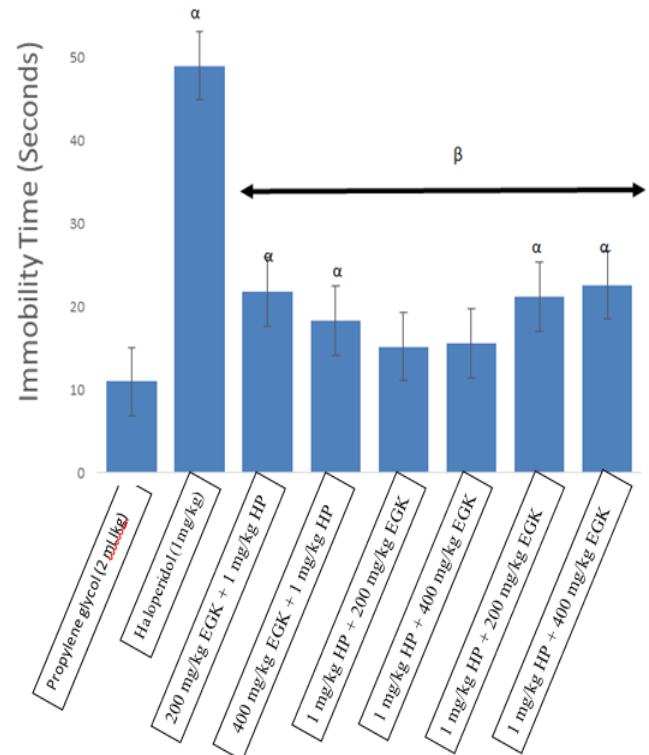


Figure 4: Effect of ethanol extract of *Garcinia kola* on immobility time in open field apparatus following haloperidol administration. Results are presented as Mean \pm SEM, $n=5$; α = significantly different from control ($p < 0.05$); β = significantly different from group II ($p < 0.05$).

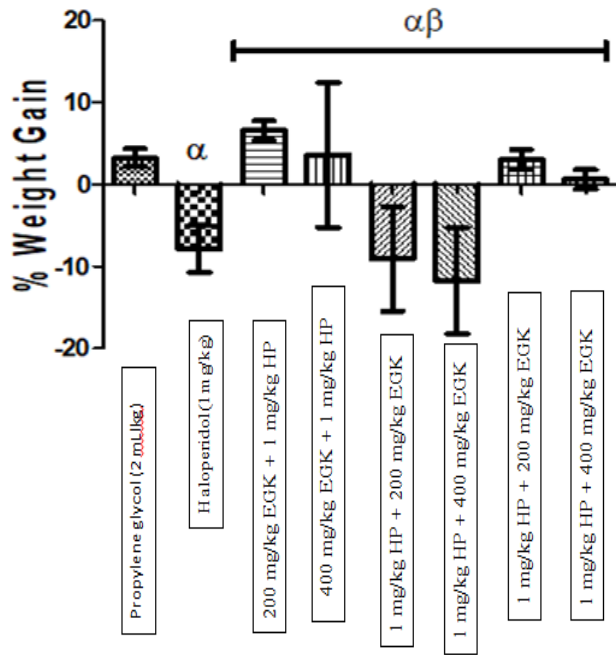


Figure 5: Effect of ethanol extract of *Garcinia kola* on body weight change following Haloperidol administration. Results are presented as Mean \pm SEM, n=5. α = significantly different from control ($p < 0.05$). β = significantly different from group II ($p < 0.05$).

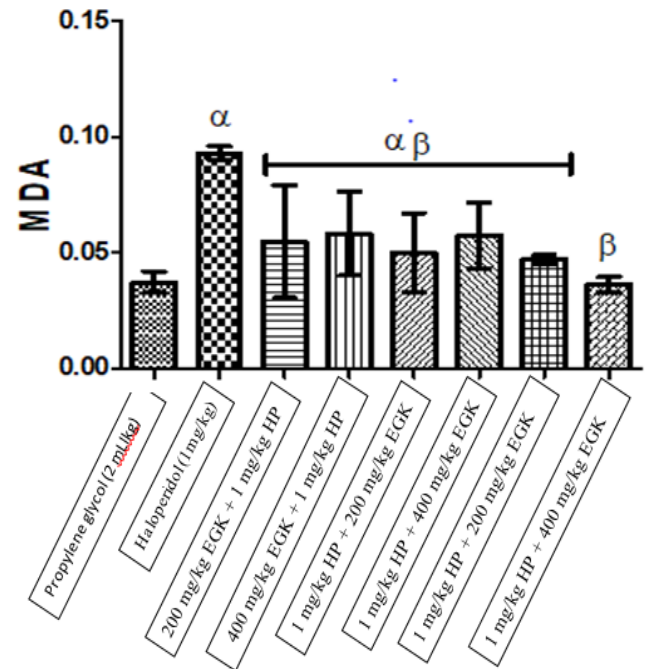


Figure 7: Effect of ethanol extract of *Garcinia kola* on MDA concentration following Haloperidol-induced catalepsy in mice. Results are presented as Mean \pm SEM, n=5. α = significantly different from control ($p < 0.05$). β = significantly different from group II ($p < 0.05$).

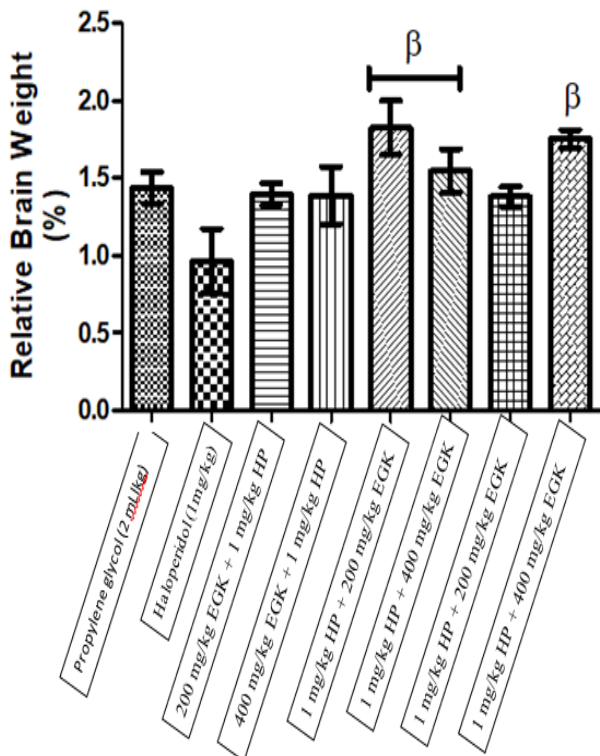


Figure 6: Effect of ethanol extract of *Garcinia kola* on relative brain weight following Haloperidol administration. Results are presented as Mean \pm SEM, n=5. β = significantly different from group II ($p < 0.05$).

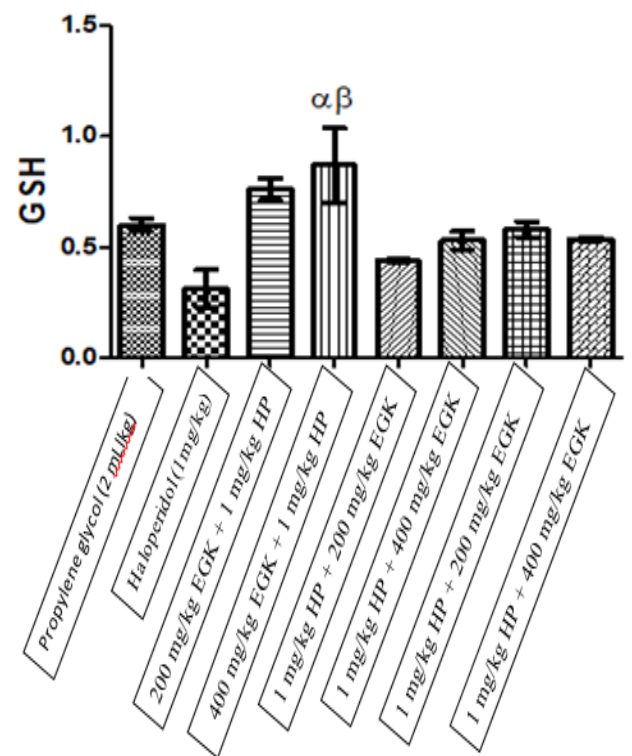


Figure 8: Effect of ethanol extract of *Garcinia kola* on GSH concentration following Haloperidol administration. Results are presented as Mean \pm SEM, n=5. α = significantly different from control ($p < 0.05$). β = significantly different from group II ($p < 0.05$).

Conclusion

In a dose-dependent manner, *Garcinia kola* extract curtailed lipid peroxidation and mitigated haloperidol-induced neurotoxicity. Further research is needed to determine the actual bioactive component that is responsible for these pharmacological effects in the brain.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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