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ORIGINAL RESEARCH article

Sorghum bicolor-based supplement reduces oxidative stress and pro-inflammatory cytokines to mitigate rotenone-induced Parkinsonian-like motor dysfunctions in rats

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Abstract: Parkinson's disease is a common movement disorder associated primarily with oxidative stress-mediated degeneration of dopaminergic neurons. Earlier studies showed that *Sorghum bicolor*-based supplement (SbS) exhibited antioxidant and neuroprotective activities and might likely rescue the death of dopaminergic neurons in Parkinson's disease. This study examined the effect of SbS on rotenone-induced Parkinsonian-like motor deficits in rats and the involvement of oxidative stress and pro-inflammatory cytokines. Rats were divided into six groups and treated orally with sunflower oil (vehicle-control), rotenone (2.5 mg/kg) alone or in combination with each dose of SbS (50, 100, and 200 mg/kg) and levodopa-carbidopa (10 mg/kg) on an alternate day for 28 days. The changes in motor functions were evaluated on day 28 and the brain concentrations of oxidative stress biomarkers and pro-inflammatory cytokines (tumor necrosis factor-alpha and interleukin-6) were determined. Rotenone caused motor deficits by impaired locomotor activity in the open field test and induced catalepsy in the bar test, which were attenuated by SbS. Rats pretreated with SbS had reduced brain levels of malondialdehyde, nitrite, and pro-inflammatory cytokines compared to rotenone controls. SbS mitigated rotenone-induced depletion of reduced glutathione and antioxidant enzymes in the rat brain. The results suggest that SbS ameliorated rotenone-induced Parkinsonian-like motor dysfunctions by reducing neuronal oxidative stress and pro-inflammatory cytokines in rats.

Introduction

Parkinson's Disease (PD) has been described as one of the most common neurodegenerative disorders after Alzheimer's disease (AD), which is characterized by the loss of dopamine neurons in the substantia nigra and the presence of Lewy bodies in surviving dopaminergic neurons [1, 2]. The motor symptoms of PD include tremors at rest, muscle rigidity, slowness of movement and postural instability [3, 4]. As PD progresses, walking becomes a difficult task for the patient due to postural instability and the tendency to fall. Thus, in the long term, the quality of life of the patient is grossly impaired and he becomes dependent on others for

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daily activities [5]. Oxidative stress and inflammation are strongly implicated in the pathophysiology of PD and the progression of the illness [5, 6]. For example, oxidative stress has been identified as the prime factor in initiating cellular injury and death of dopaminergic neurons in PD [7, 8]. Studies have reported elevated levels of oxidative stress in postmortem brain tissue of patients with PD, including increased cholesterol lipid hydroperoxides in the substantia nigra [9-12]. Increased cytoplasmic 8-hydroxy-guanosine immunoreactivity and oxidative damage to several brain mitochondrial complex I proteins accompanied by decreased glutathione in neurons of the substantia nigra have been reported [12, 13]. The findings of reduced antioxidant molecules and high concentrations of oxidized lipids and protein in the brains of individuals with PD further confirmed the key role of oxidative stress in the pathology of the illness [6, 12, 13]. Oxidative stress-mediated injury to neuronal cells evokes the release of pro-inflammatory cytokines, thereby linking oxidative stress and inflammation as co-conspirators in the pathogenesis of PD [2, 5, 14, 15]. The key role of oxidative stress and neuroinflammation in the pathophysiology of PD has also been reinforced by the findings that rotenone, a neurotoxin, is widely used to replicate the behavioral and biochemical changes including synucleinopathies akin to PD pathology. Specifically, rotenone is known to cause Parkinsonian-like symptoms through the formation of free radicals that lead to impairment of mitochondrial electron transport machinery [3]. Thus, it has been proposed that since a multifactorial cascade of pathogenic events triggered by oxidative stress causes cell death in PD, the neuroprotective strategy might be a better option for treating PD [14, 16]. Accordingly, oxidative and neuroinflammation have become important advancements and promising targets, with antioxidant and anti-inflammatory agents as promising, reliable therapeutic interventions [17, 18].

Sorghum bicolor-based supplement (SbS) is a supplement obtained from the leaf sheath of *Sorghum bicolor* (Poaceae) that has been shown to exhibit potent antioxidant, neuroprotective and anti-inflammatory activities [19-21]. SbS improved neurological deficits in rats with ischemic stroke by reducing of brain contents of pro-inflammatory cytokines and expression of NF-kB immunopositive cells [22, 23). In a recent study using *Drosophila melanogaster*, SbS extended the lifespan and improved the motor function of the flies through augmentation of the antioxidant status [23]. In this study, we examined the effect of SbS on rotenone-induced Parkinsonian-like motor deficits in rats and the probable involvement of oxidative stress, and pro-inflammatory cytokines.

Materials and methods

Chemicals: Rotenone, thiobarbituric acid (TBA) were purchased from Sigma Aldrich (Germany), 5,5'-dithio-bis-2-nitrobenzoic acid (Ellman's reagent) and acetylthiocholine iodide from Sigma Aldrich (USA). ELISA kits for rats' tumour necrosis factor-alpha and interleukin-6 from Biolegend (USA). The levodopa-cabidopa (LD-CD) was a product of Merck & Co, Inc (USA).

*Experimental animals***:** Male Albino Wistar rats (weight: 170 g - 200 g, age: 10-13 weeks) used in this study were obtained from the Central Animal House, University of Ibadan, Nigeria. Rats were acclimatized in the Department of Pharmacology and Therapeutics Animal Holding Facility for two weeks before the study. They were housed in cages with free access to a standard rodent pellet diet (Vital Feeds, Jos, Nigeria) and water *ad libitum*. The procedures were by the National Institute of Health (NIH Publication No 8523, revised 1981) guidelines for the Care and Use of Laboratory Animals. Approval was obtained from the University of Ibadan Animal Care and Use Research Ethics Committee (UI-ACUREC/20/0055).

Preparation of SbS and rotenone: SbS was obtained from Health Forever Products Ltd, Lagos, Nigeria and was prepared as described [20]. Briefly, on the experimental day, 500 mg of SbS was dissolved in 25 mL of water to obtain 20 mg/mL. The doses of 50, 100 and 200 mg/kg were selected based on an earlier study [22]. Rotenone was prepared according to a previous study [24]. Thus, rotenone was initially dissolved in dimethyl

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sulfoxide (DMSO) and the solution was diluted in sunflower vegetable oil to obtain 0.25 mg per mL. The intraperitoneal dose of 2.5 mg/kg of rotenone was chosen based on an earlier study [24].

Effect of SbS on rotenone-induced Parkinsonian-like symptoms in rats: The effect of SbS on rotenone-induced Parkinsonian-like symptoms was studied in rats according to a previous study [24]. Thus, rats were randomly divided into six groups (n=7). Rats in group 1, which served as vehicle control, received sunflower oil (10 mL/kg, p.o.), group 2 had sunflower oil (rotenone control), groups 3-5 were pre-treated SbS (50, 100 and 200 mg/kg, p.o.) while the last group received LD-CD (10 mg/kg, p.o.), daily for 28 days. 30 min after each pretreatment, rats in groups 2-6 received rotenone (2.5 mg/kg, i.p.) on alternate days for 28 days. Afterward, the test for locomotion and catalepsy using an open field and bars, respectively, were carried out to evaluate the motor functions of the rats on day 28.

Procedures for evaluation of motor functions

Test for spontaneous motor activity (SMA): The SMA was assessed using an open-field test. The open-field apparatus consists of plywood (72x72x36 cm) with the floor divided into sixteen squares, 18x18 cm [25]. The rats were placed individually at the center of the chamber, and the number of lines crossed, and duration of ambulation were recorded for five minutes using a video camera [25].

Test for catalepsy: The effect of SbS on rotenone-induced catalepsy was investigated according to the modified method [26]. The test was done by placing the forelimbs of each rat on a horizontal plane wood surface (H: 6, W: 4, and L: 16 cm) and the duration of akinesia (the period the rat remained in one position, before initiating any active movement) was recorded for five minutes.

Preparation of brain tissues for biochemical assays: Immediately after the behavioral studies, the rats were euthanized using diethyl ether and each of the isolated brains was weighed and rinsed with 10.0% w/v sodium phosphate (0.1 M; pH 7.4). Each brain tissue was homogenized and centrifuged, and the supernatant was collected for the biochemical parameters [22].

Estimation of oxidative stress biomarker and nitrite content: The malondialdehyde (MDA) contents in the brain regions were estimated using the procedure of thiobarbituric reacting substance (TBARS) [27]. The striatal MDA content was calculated using a molar extinction coefficient of $1.56x10.0^5$ per M per cm and expressed as µmol MDA per g tissue. The determination of nitrite content is estimated as described [28]. The absorbance was read at 540 nm and the nitrite in the striatum was estimated from the standard curve of sodium nitrite (0.0 M-100 M).

Estimation of antioxidant biomarkers: The brain-reduced glutathione (GSH) was assayed as described previously and expressed as µM GSH per g tissue [29]. The method described by Goth [30] was utilized for the determination of catalase activity and expressed as µmoles of hydrogen peroxide decomposed (Unit/mg protein). A method of Misra and Fridovich [31] was used for the estimation of superoxide dismutase (SOD) activity (Unit/mg protein). Protein content was estimated using the procedure of Lowry et al. [32].

Determination of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) contents: The brain concentrations of TNF-α and IL-6 were determined using ELISA kits according to the manufacturer's instructions guide. The concentrations were determined from their standard curves respectively and expressed as pg/mg protein.

Statistical analysis: After normality and homogeneity data checks, data were expressed as mean±S.E.M, and analyzed using Graph Pad Prism software version 9.00 (San Diego, CA, USA). The analysis of data was done using one-way ANOVA, followed by Bonferroni post-hoc test. A p-value less than 0.05 was considered significant.

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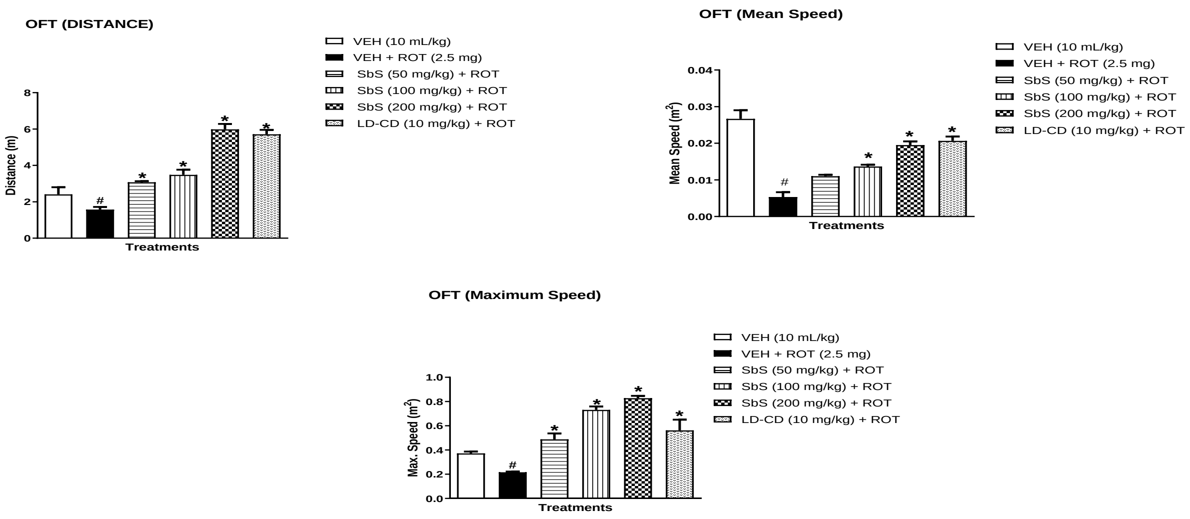
Results

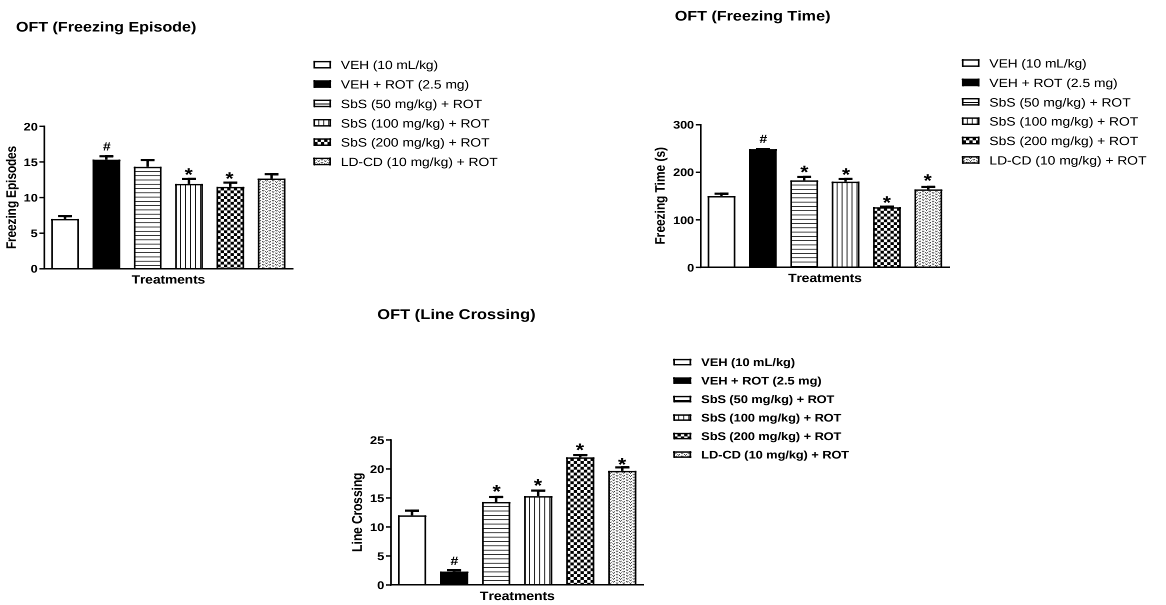
SBS reduces rotenone-induced locomotor deficits: The effects of SbS on rotenone-induced Parkinsonian-like motor features in rats are shown in **Figures 1** and **2**. **Figure 1** showed that 2.5 mg/kg rotenone reduced the distance traveled [$F_{(5, 18)}$=46.84, p<0.001] and the speed [$F_{(5, 18)}$=34.69, p<0.001] in navigating the open field chamber relative to controls. As shown in **Figure 2**, 2.5 mg/kg rotenone increased the freezing episodes (periods in which the rat stops movement) [$F_{(5, 18)}$=26.09, p<0.001] and the freezing time (period of absence of movement) [$F_{(5, 18)}$ =74.12, p<0.001], and the number of lines crossed when compared with controls [$F_{(5, 18)}$=98.72, p<0.001]. However, an oral administration of 100 mg/kg and 200 mg/kg SbS or 10.0 mg/kg LD-CD significantly improved rat motor functions when compared with rotenone (**Figures 1** and **2**).

Figure 1: *Sorghum bicolor* supplement improves motor functions in rats exposed to rotenone



Bars are mean±S.E.M. $^{\#}$p<0.05 versus vehicle, *p<0.05 versus rotenone (ANOVA followed by Bonferroni test)
VEH=vehicle, SbS=Sorghum bicolor supplement, LD-CD=levodopa-carbidopa

Figure 2: *Sorghum bicolor* supplement mitigated rotenone-induced freezing behaviors and impaired rat locomotion



Bars are mean±S.E.M. $^{\#}$p <0.05 versus vehicle, *p<0.05 versus rotenone (ANOVA followed by Bonferroni test)
VEH=vehicle, SbS=Sorghum bicolor supplement, LD-CD=levodopa-carbidopa

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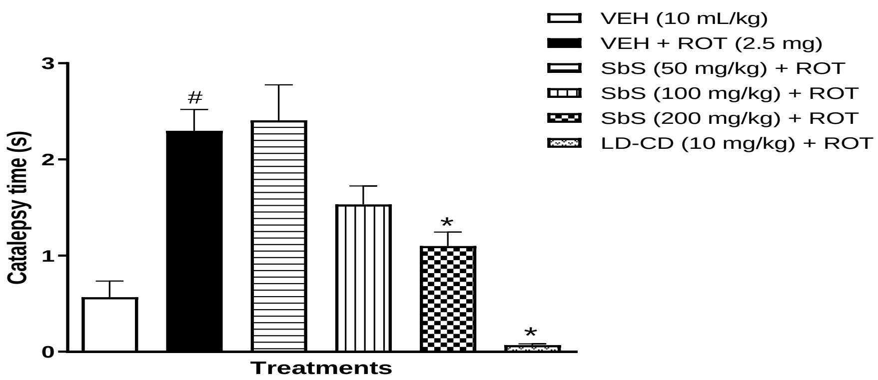
SBS attenuates rotenone-induced catalepsy: In **Figure 3**, intraperitoneal injection of 2.5 mg/kg rotenone caused catalepsy, evidenced by a significant increase in latency to initiation of movement relative to control. An oral dose of 200 mg/kg SbS or 10.0 mg/kg LD-CD highly significantly prevented catalepsy relative to the rotenone group [$F_{(5, 36)}$=19.36, p<0.001]. In **Figure 3**, lower doses of 50.0 mg/kg SbS to 100 mg/kg SbS could not alter rotenone-induced cataleptic condition.

SBS decreases brain malondialdehyde (MDA): Intraperitoneal injection of 2.5 mg/kg rotenone significantly elevated MDA concentrations of the hippocampus (HIP), prefrontal cortex (PFC) and striatum (STR) regions of rats relative to the control (**Figure 4**). As presented in **Figure 4**, 100 mg/kg and 200 mg/kg of SbS or 10.0 mg/kg LD-CD given orally significantly suppressed MDA concentrations in these brain regions of rotenone-treated rats. [HIP: $F_{(5, 20)}$=15.36, p<0.001; PFC: $F_{(5, 20)}$=9.688 p<0.001; STR: $F_{(5, 20)}$=7.446, p<0.001].

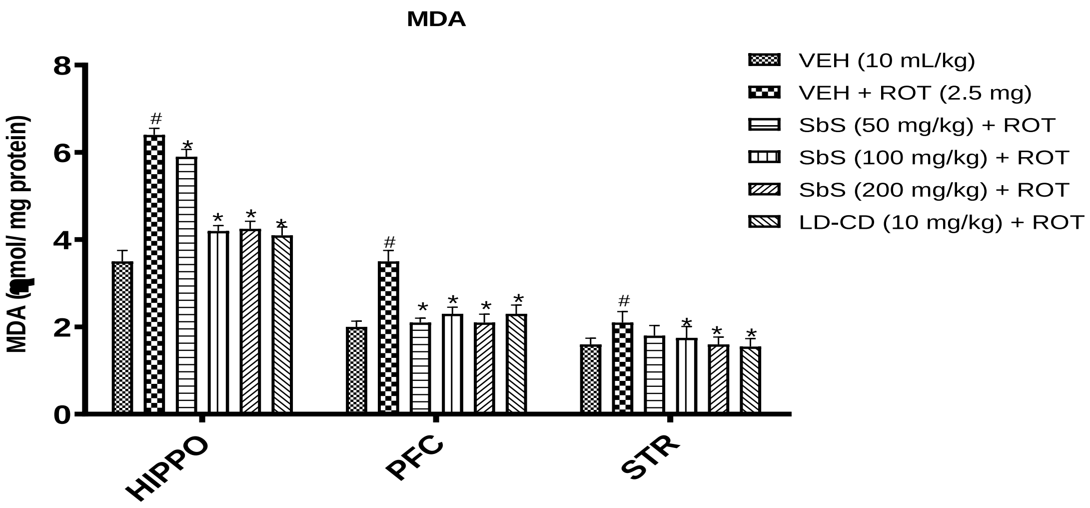
SBS increases glutathione (GSH) in rotenone-treated rats: As presented in **Figure 5**, 2.5 mg/kg rotenone significantly decreased GSH levels in the hippocampus and striatum of rats relative to the control. Though, 100 mg/kg and 200 mg/kg SbS or 10.0 mg/kg LD-CD significantly mitigated rotenone-induced GSH depletion (**Figure 5**) [HIP: $F_{(5, 20)}$=14.79, p<0.001; STR: $F_{(5, 21)}$=14.37, p<0.001].

Figure 3: *Sorghum bicolor* supplement attenuates rotenone-induced catalepsy in rats



*Bars are mean±S.E.M. #p<0.05 versus vehicle, *p<0.05 versus rotenone (One-way ANOVA followed by Bonferroni test)*
VEH=vehicle, SbS=Sorghum bicolor supplement, LD-CD=levodopa-carbidopa

Figure 4: *Sorghum bicolor* supplement decreases rotenone-induced elevation of malondialdehyde content in the hippocampal, prefrontal cortex, and striatum regions of rats



*Bars are mean±S.E.M. #p<0.05 versus vehicle. *p<0.05 versus rotenone (ANOVA followed by Bonferroni test)*
VEH=Vehicle, SbS=Sorghum bicolor supplement, LD-CD=Levodopa-carbidopa

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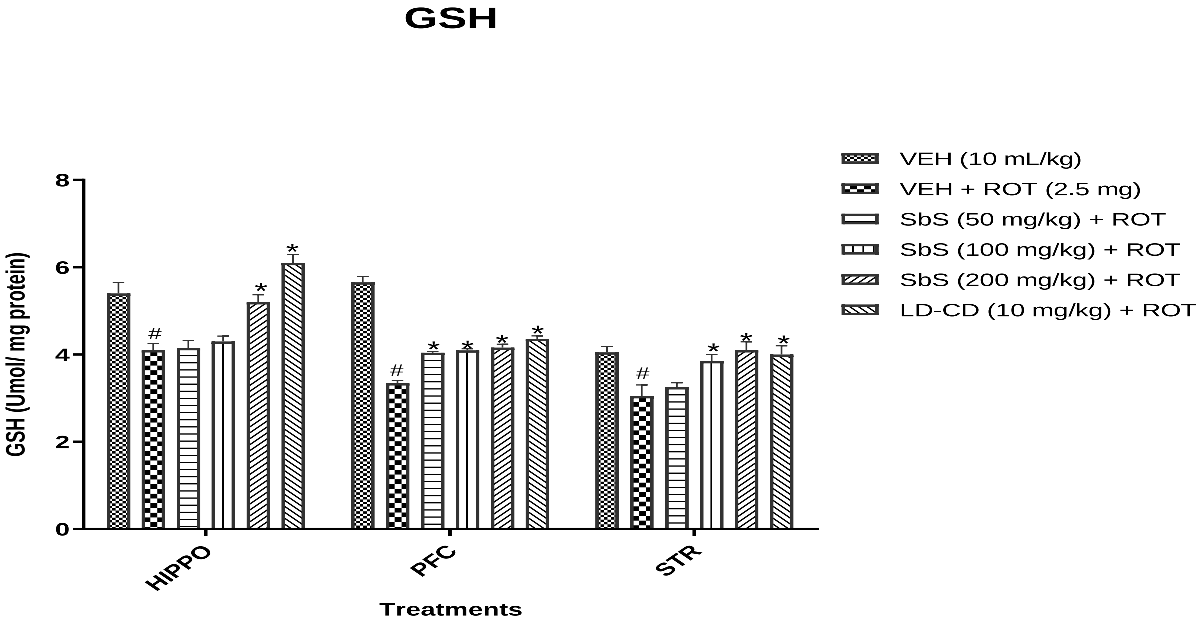
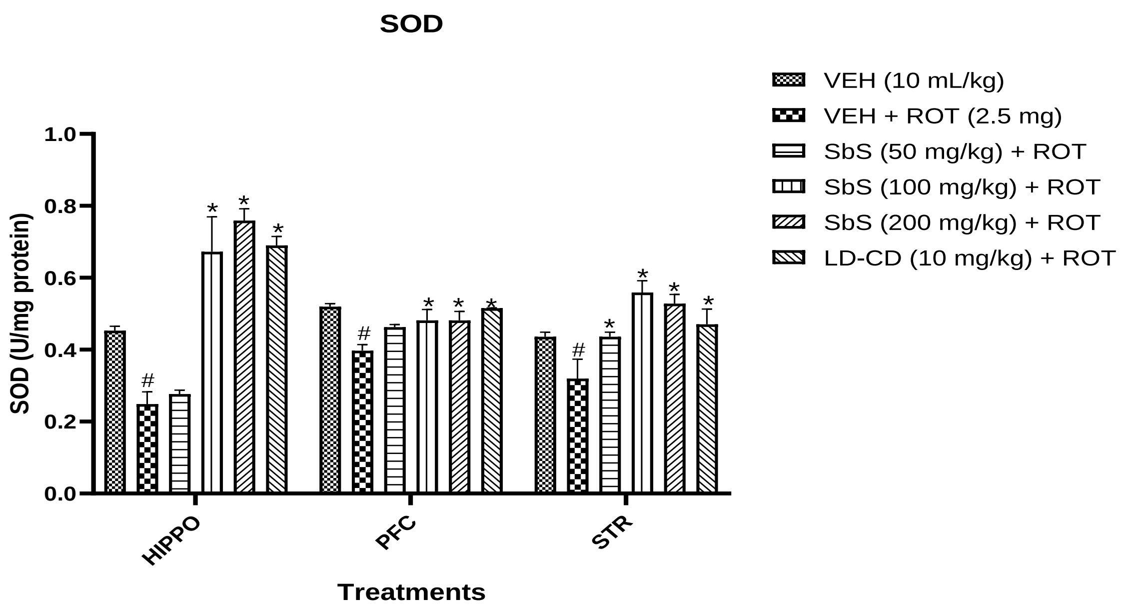
Figure 5: *Sorghum bicolor* supplement elevates glutathione (GSH) levels in the hippocampus and striatum of rats treated with rotenone



*Bars are mean±S.E.M. #p<0.05 versus vehicle. *p<0.05 relative to rotenone (ANOVA followed by Bonferroni test)*
VEH=vehicle, SbS=Sorghum bicolor supplement, LD-CD=levodopa-carbidopa

SBS boosts neuronal antioxidant activity in rotenone-treated rats: The effects of SbS on antioxidant enzymes (superoxide dismutase-SOD and catalase) in specific brain regions of rats injected with rotenone are presented in **Figures 6** and **7**. Intraperitoneal dose of rotenone (2.5 mg/kg) caused significant suppression of SOD and catalase activities in specific brain regions of rats when compared with control. Though, 100 mg/kg and 200 mg/kg SbS or 10.0 mg/kg LD-CD significantly increased SOD and catalase activity (**Figure 6** and **7**) [$F_{(5, 59)}$=113.9, p<0.001].

Figure 6: *Sorghum bicolor* supplement increases prefrontal cortex and striatum superoxide dismutase (SOD) in rats exposed to rotenone



*Bars are mean±S.E.M. #p<0.05 versus vehicle. *p<0.05 versus rotenone (ANOVA followed by Bonferroni test)*
VEH=Vehicle, SbS=Sorghum bicolor Supplement, LD-CD=Levodopa-carbidopa

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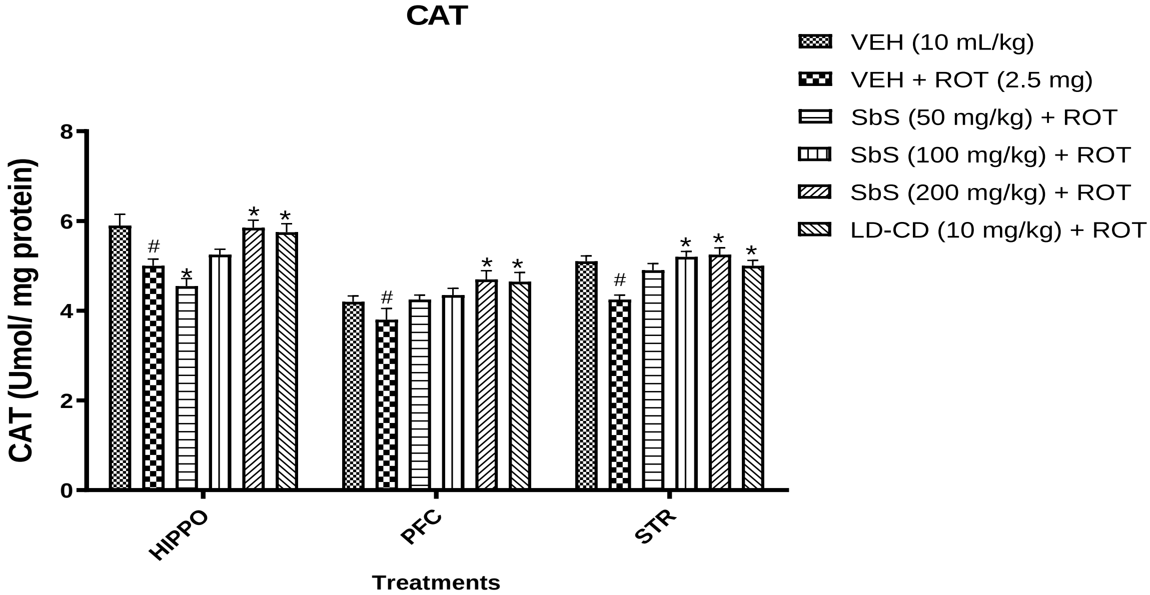
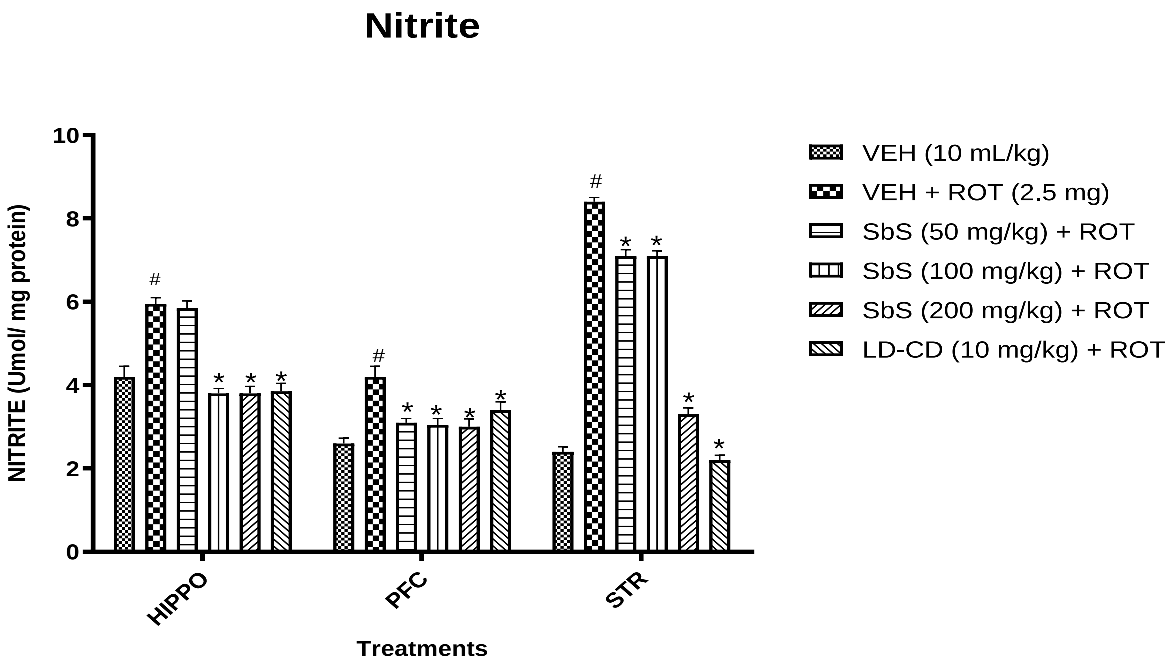
Figure 7: *Sorghum bicolor* supplement increases hippocampal, prefrontal cortex, and striatal catalase (CAT) activity of rats treated with rotenone



*Bars are mean±S.E.M. #p<0.05 versus vehicle. *p<0.05 versus rotenone (ANOVA followed by Bonferroni test) VEH=vehicle, SbS=Sorghum bicolor supplement, LD-CD=levodopa-Carbidopa*

SBS reduces nitrite contents of rotenone-treated rats: In **Figure 8**, 2.5 mg/kg rotenone significantly increased nitrite concentrations in the hippocampus, striatum and prefrontal cortex of rats compared with the controls. However, 100 mg/kg and 200 mg/kg SbS or 10.0 mg/kg LD-CD significantly reduced nitrite contents in these brain regions of rats relative to rotenone (**Figure 8**) [HIP: $F_{(5, 20)}$=12.87, p<0.001; PFC: $F_{(5, 20)}$=17.29, p<0.001; STR: $F_{(5, 21)}$=53.08, p<0.001].

Figure 8: *Sorghum bicolor* supplement decreases hippocampal, prefrontal cortex, and striatal nitrite concentrations of rotenone-treated rats



*Bars are mean±S.E.M. #p<0.05 versus vehicle. *p<0.05 versus rotenone (ANOVA followed by Bonferroni test) VEH=vehicle, SbS=Sorghum bicolor supplement, LD-CD=levodopa-carbidopa*

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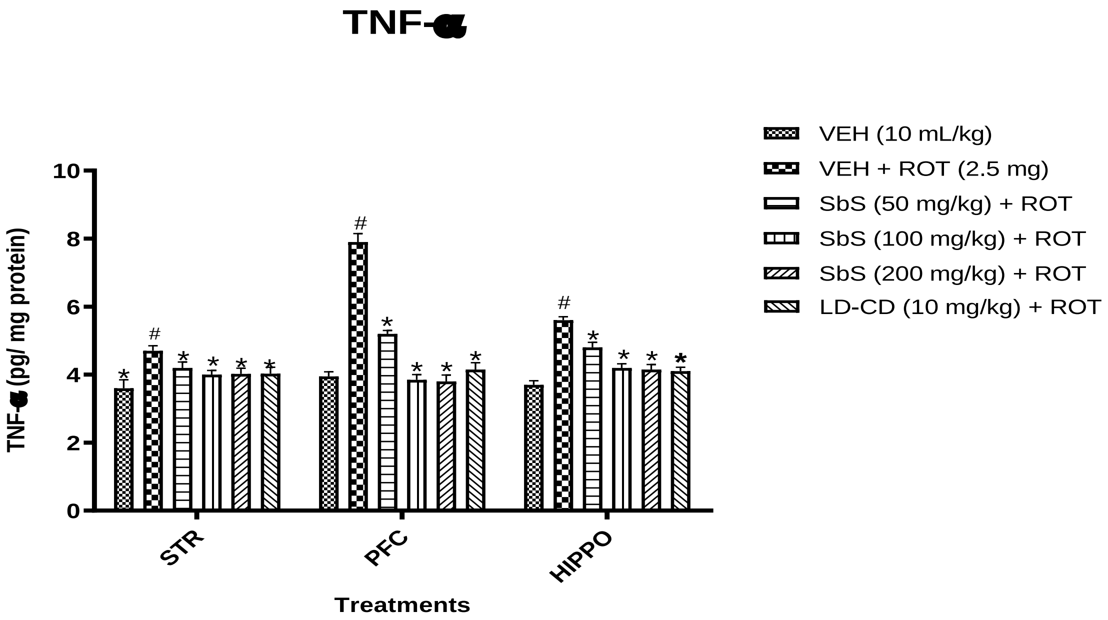
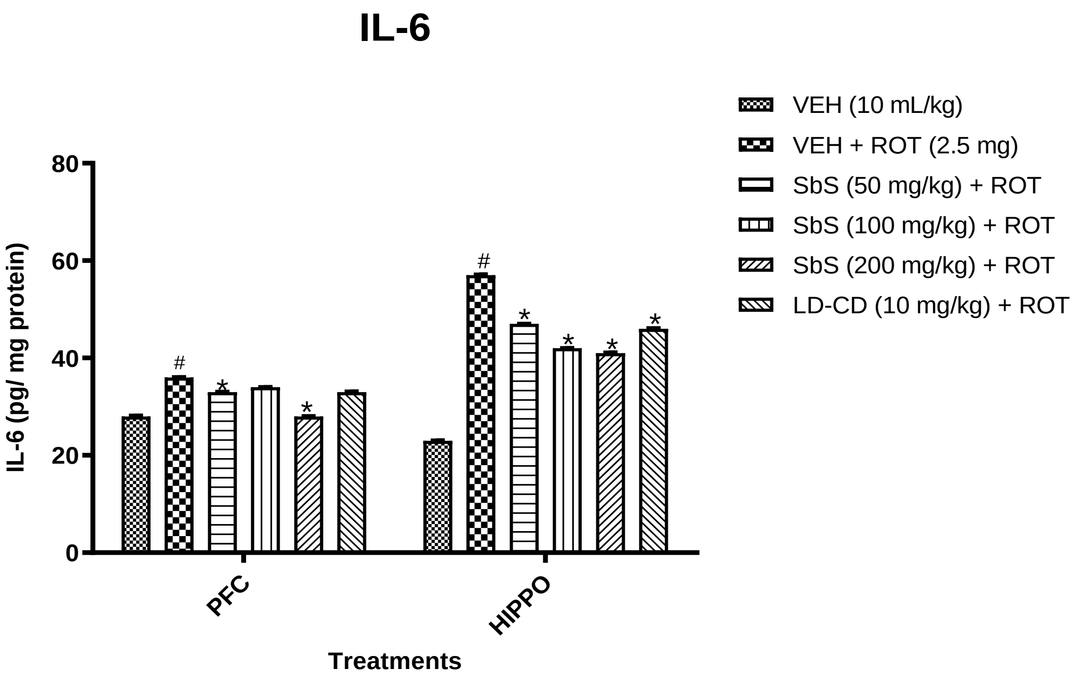
SBS reduces tumornecrosis factor-α and interleukin-6 contents of rats given rotenone: Rotenone in a dose of 2.5 mg/kg caused a significant increase in the concentrations of pro-inflammatory cytokines (TNF-α and IL-6) in the striatum, prefrontal cortex, and hippocampus of rats relative to controls (**Figures 9** and **10**). However, 100 mg/kg and 200 mg/kg SbS significantly reduced the concentrations of these pro-inflammatory cytokines in these brain regions of rats relative to rotenone **(Figures 9** and **10)**.

Figure 9: *Sorghum bicolor* supplement reduces striatal, prefrontal cortex, and hippocampal tumor necrosis factor (TNF-α) contents of rats exposed to rotenone



*Bars are mean±S.E.M. #p<0.05 versus vehicle. *p<0.05 versus rotenone (ANOVA followed by Bonferroni test) VEH=vehicle, SbS=Sorghum bicolor supplement, LD-CD=levodopa-carbidopa*

Figure 10: *Sorghum bicolor* supplement reduces prefrontal cortex and hippocampal interleukin-6 (IL-6) levels of rats exposed to rotenone



*Bars are mean±S.E.M. #p<0.05 versus vehicle. *p<0.05 versus rotenone (ANOVA followed by Bonferroni test) VEH=vehicle, SbS=Sorghum bicolor supplement, LD-CD=levodopa-carbidopa*

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Discussion

It is well established that intraperitoneal injection of rotenone induces parkinsonian-like motor deficits characterized by impaired locomotion, catalepsy and postural instability in rodents [3, 33-36]. Thus, it has served as an animal model widely used for the evaluation of novel agents with potential antiparkinsonian-like activity [3, 34-36]. In this study, the video analysis in the open field test confirmed that rotenone caused impairment of locomotor functions in rodents, evidenced by reduced distance traveled, number of lines crossed, navigational speed and increased freezing episodes/freezing time in the open field chamber. However, SbS at high doses attenuated rotenone-induced locomotor deficits in rats, suggesting potential benefits in ameliorating the motor symptoms associated with PD. Indeed, impairment of motor functions is a prominent feature of patients with PD and rats treated with rotenone [3, 4, 8, 35]. This impairment results in a reduction in voluntary movements and difficulty in initiating movement (akinesia) due to muscle rigidity [3]. The test for catalepsy is a common neurobehavioral feature that is widely measured in rodents that closely resemble akinesia in persons suffering from PD [37]. Catalepsy is defined as a state of motor dysfunction leading to difficulty in initiating voluntary movement characterized by the tendency of the limbs of the rats to remain in whatever position they are placed [37]. The results of the current study also support earlier investigation [37] which showed that intraperitoneal injection of rotenone-induced marked cataleptic behavior in rodents. Thus, the findings that SbS attenuated rotenone-induced catalepsy further suggest that it might offer beneficial effects in movement disorders pathognomonic of PD. It is worth noting that rotenone, a well-known neurotoxin, has been reported to cause neuropathological changes akin to PD via induction of oxidative stress due to disturbances in the mitochondrial electron transport system [3, 33, 34, 36]. Previous investigations have identified raised levels of oxidative stress and pro-inflammatory cytokines in the brain of animals after exposure to rotenone [3], and metabolic degradation of neuronal lipids and DNA [33, 38, 39]. Production of reactive oxygen and nitrergic species is well-known to be exacerbated by mitochondrial dysfunctions, microglia activation, neurodegeneration, and impaired antioxidant response mechanisms [3, 6, 38, 39]. Therefore, rotenone-induced depletion of endogenous antioxidant molecules (glutathione, catalase and superoxide dismutase) may contribute to its toxicity on dopaminergic neurons [38, 39]. It is known that a deficiency of striatal GSH has been reported in the literature and is believed to contribute to severe neuropathological derangements in PD [40]. In this study, SbS reduces MDA and nitrite concentrations and boosts antioxidant molecules in specific brain regions of rotenone-treated rats. Thus, these findings suggest that SbS exhibited an antioxidant defense protective effect against rotenone-induced motor deficits in rats.

Earlier investigations had also identified raised brain concentrations of pro-inflammatory cytokines in rodents exposed to rotenone [33, 36-38]. Indeed, several studies have shown that rotenone inhibited mitochondrial complex-I resulting in increased microglial activation, depletion of the antioxidant defense system and release of pro-inflammatory cytokines in various brain regions [33, 38]. Oxidative stress-mediated neuronal injury further releases pro-inflammatory cytokines, hence supporting the notion that oxidative stress and inflammation are co-conspirators in the demise of dopaminergic fibers [6, 38, 39]. It is interesting to state that SbS reduced the brain concentrations of pro-inflammatory cytokines induced by rotenone in rats. This finding is in agreement with earlier studies that showed that SbS mitigated neurological disorders in rats subjected to ischemic stroke via suppression of oxidative stress and pro-inflammatory cytokines [22]. Thus, the ability of SbS to reduce rotenone-induced Parkinsonian-like motor deficit in rats might also be related to its antioxidant and anti-inflammatory activities. Besides, it is also pertinent to mention that several studies have shown that SbS contains bioactive constituents, including apigenidin, apigenin, naringenin, and luteolin [19], with proven antioxidant, anti-inflammatory and neuroprotective activities [2, 16, 21, 41, 42].

Although previous studies have shown that SbS produces its most effective action between the doses of 50 mg/kg and 100 mg/kg, in this study, we intriguingly observed that SbS demonstrated a dose-dependent effect,

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which suggests a unique therapeutic potential of SbS in the management of PD-like neuropathologies. As to whether SbS exerts superiority over LD-CD as a potential agent for motor impairment associated with rotenone, needs further investigation. However, in the context of safety and tolerability, it is important to mention that SbS is generally regarded as very safe for human consumption as it forms a very important part of our diets as a vegetable. Our previous research found that SbS is most effective at doses between 50 mg/kg and 100 mg/kg [22]. This study observed a dose-dependent effect of SbS of more than 100 mg/kg, indicating its unique stereoselective therapeutic potential against PD-like neuropathologies. However, more investigation is needed to determine if SbS is superior to LD-CD in addressing motor impairment associated with rotenone. It's worth noting that SbS is generally considered safe for human consumption and is a significant part of our diets as a vegetable. Interestingly, it was recently shown that SbS ameliorated liver and kidney impairment induced by aflatoxin-1 [43], a potent genotoxic hepatocarcinogen that causes up-regulation of alpha-synuclein, neuroinflammation, and degeneration of dopaminergic neurons [44]. However, the role(s) of phytochemicals in the anti-Parkinsonian-like effect of SbS requires further investigations.

Conclusion: This study suggests that SbS mitigated rotenone-induced parkinsonian-like motor dysfunctions by reducing oxidative stress and pro-inflammatory cytokines in rats indicating its therapeutic potential in movement-related disorders.

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