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Original Article

Investigating the neuroprotective, anti-inflammatory, and antioxidant effects of *Agaricus bisporus* mushroom in the Rat Model of Parkinson's Disease

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ABSTRACT

Background: Due to the antioxidant and anti-inflammatory properties of Agaricus bisporus mushrooms, there is potential for positive effects in preventing Parkinson's disease. This study aims to investigate the neuroprotective effects of Agaricus bisporus mushrooms in a rotenone-induced model of Parkinson's disease in rats.

Methods: Rats were divided into five groups: control (CON), rotenone (ROTE), and three groups receiving rotenone and different doses of A. bisporus mushroom (ABM 100, ABM 200, and ABM 300) at doses of 100, 200, and 300 mg/kg, respectively, administered daily for 21 days. Behavioral responses were assessed using the open field test and rotarod test, and various parameters including striatal dopamine, IL-1β, IL-6, TNF-α, malondialdehyde (MDA), reduced glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT) were measured. Additionally, the expressions of Drp-1, PGC1α, and TFAM were evaluated.

Results: The results demonstrated that rotenone significantly reduced ambulation, rearing, grooming, and increased immobility time compared to the control group (P=0.001). Rotenone also decreased striatal dopamine content, GSH, SOD, CAT, and increased pro-inflammatory cytokine concentrations compared to the control group (P=0.001). Furthermore, rotenone decreased the expression of Drp-1 and increased the expressions of PGC1α and TFAM compared to the control group (P=0.001).

Conclusion: The use of the mushroom at higher concentrations (200 mg/kg and 300 mg/kg) reversed the effects of rotenone, suggesting that this mushroom may be utilized for preventing Parkinson's disease at higher doses.

KEYWORDS: Parkinson's Disease, Mushroom, Inflammation, Rat

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1. Introduction

Parkinson's disease, a progressive nervous system disorder affecting movement, manifests diverse signs and symptoms [1]. Its onset is characterized by mild and often unnoticed early symptoms, typically starting on one side and later extending to both sides, with more pronounced effects on the initial side [2]. Primarily impacting dopamine-producing neurons in the substantia nigra region of the brain, Parkinson's disease disrupts the crucial role of dopamine in regulating body movement, leading to various symptoms [3-6]. The exact cause remains unknown, although a combination of genetic and environmental factors is believed to contribute [7, 8]. Dopamine acts as a messenger in the brain and nervous system, crucial for coordinating body movements [9, 10]. Reduction in dopamine levels due to cell damage in the substantia nigra leads to abnormal and slow movements, marking the onset of Parkinson's symptoms [11]. Nerve cell loss occurs gradually, with symptoms emerging when approximately 80% of neurons in the substantia nigra have been destroyed [12]. Oxidative stress, often induced by stress and injuries, triggers inflammation, adversely affecting normal brain function [13, 14]. Detectable signs of oxidative damage precede nerve cell destruction in Parkinson's disease [15], highlighting the potential roles of inflammation and oxidation in the disease. While no cure exists, medications can alleviate symptoms, and certain natural agents show promise in symptom reduction. *Agaricus bisporus*, commonly known as the white button mushroom, is a rapidly growing fungus with global popularity for its nutritional richness low in carbohydrates and fats, high in protein, amino acids, polysaccharides, minerals, multivitamins, and phytochemical components [16, 17]. Notably, it possesses antioxidant and anti-inflammatory properties [18-20]. Given these characteristics, this study aims to explore the neuroprotective effects of *Agaricus bisporus* mushrooms in a rotenone-induced rat model of Parkinson's disease, focusing on its anti-inflammatory and antioxidant properties.

2. Materials and Methods

2.1. The preparation of mushroom

The mushroom was prepared and chemical analyses showed its composition as follows: protein (47.00%), carbohydrate (18.00%), fat (3.60%), ash (10.05%), fiber (15.80%) and moisture (3.20%).

2.2. Animals

Sixty male adult Wistar rats, aged 8 weeks, were distributed across six groups, with meticulous attention to minimizing pain and stress during the experimental procedures. The rats had ad libitum access to water and feed, and environmental conditions, including temperature and humidity, were maintained within optimal ranges for their well-being. The animals were subjected to a 12-hour dark/12-hour light cycle. Group 1, designated as the control group (CON), received 1.00% dimethylsulfoxide (DMSO; Sigma-Aldrich, St. Louis, MO, USA) at a dose of 0.1 mL/100 g subcutaneously every other day. Additionally, Tween 80 (10% v/v) was administered daily for three weeks. Group 2 (ROTE) received rotenone (Sigma-Aldrich), dissolved in 1% DMSO, subcutaneously every other day at a dose of 1.5 mg/kg for three weeks. The remaining groups (ABM 100, ABM 200, and ABM 300) received A. bisporus mushroom at doses of 100, 200, and 300 mg/kg, respectively, administered daily for 21 days. The mushroom administration occurred 1 hour before rotenone administration.

2.3. Behavioral responses

At the conclusion of the study on day 21, the open field test and rotarod test were conducted following established protocols as described by previous researchers [21]. For the open field test, a square wooden box measuring 80 × 80 × 40 cm, featuring red walls and a black floor divided into a 4 × 4 grid of 16 equal squares with white lines, was employed. Various parameters were assessed, including latency time (duration of immobility), ambulation frequency (horizontal movement), grooming frequency (instances of face scratching, hind limb washing, and forelimb licking), and rearing frequency (vertical movement).

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These behaviors were recorded for each rat over a 5-minute period. In the rotarod test, the rats' motor coordination and balance were evaluated using a rotarod apparatus with dimensions of 90 cm in height, a 3 cm diameter, and a rotation speed of 25 rpm. The latency to fall off the rotarod was recorded as a measure of motor coordination.

2.4. Biochemical analyses

At the termination of the study, the rats were humanely euthanized through decapitation, and the right striatum (ipsilateral to the lesion) was promptly dissected on ice. Striatal dopamine content was determined using commercial kits and expressed as ng/mg protein. Additionally, the concentrations of pro-inflammatory cytokines, namely IL-1β, IL-6, and TNF-α, were measured using commercial kits. Oxidative parameters in homogenates from the same brain region were assessed to evaluate malondialdehyde (MDA) levels, reduced glutathione (GSH) concentrations, and the enzyme activities of superoxide dismutase (SOD) and catalase (CAT).

2.5. The qPCR

For qPCR analysis, RNA extraction was performed using an RNA extraction kit (Cinnagen Inc., Iran) following the provided procedure instructions. The quality and purity of the extracted RNA were evaluated through electrophoresis visualization of 28S and 18S ribosomal RNA bands and determining the A260/A280 ratio using a NanodropTM spectrophotometer. Subsequently, the extracted RNA was stored at -80 °C for cDNA synthesis. The protocols and primers for Drp-1, PGC1α, and TFAM were adopted from previous studies [22].

2.6. Data analysis

The data were evaluated for normality and because the data were normal, these were analyzed with the help of ANOVA pathway. All the analyses were conducted and graphs were depicted with the help of Graph Pad Prism software (version of 6.07).

3. Results

3.1. Behavioral responses

Figure 1 presents the outcomes of the investigation into the impact of A. bisporus mushroom on rotenone-induced changes in motor activity and coordination, as assessed through the open field and rotarod tests. Rotenone administration resulted in a significant reduction in the number of ambulations, rearings, grooming instances, and increased falling time, along with elevated immobility time compared to the control group (P=0.001). However, the administration of A. bisporus mushroom at doses of 200 mg/kg and 300 mg/kg significantly reversed these effects, leading to increased ambulation, rearing, grooming, and falling times, along with a decrease in immobility time compared to the ROTE group (P=0.001). Notably, the 100 mg/kg dose did not yield significant effects.

3.2. Striatal dopamine content

Figure 2 illustrates the results for the effects of A. bisporus mushroom on striatal dopamine content in rotenone-induced Parkinson rats. The results showed that rotenone significantly decreased striatal dopamine content compared with control group (P=0.001). The results showed that A. bisporus mushroom (200 mg/kg and 300 mg/kg) significantly increased striatal dopamine content compared with ROTE group (P=0.001). It did not have significant effects in 100 mg/kg.

3.3. Inflammatory responses

Figure 3 portrays the outcomes of the study examining the influence of A. bisporus mushroom on the content of striatal pro-inflammatory cytokines in rats with rotenone-induced Parkinson's disease. The

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results indicated a significant increase in striatal pro-inflammatory cytokines content due to rotenone compared to the control group (P=0.001). Conversely, the administration of A. bisporus mushroom at doses of 200 mg/kg and 300 mg/kg significantly attenuated the striatal pro-inflammatory cytokines content in comparison to the ROTE group (P=0.001). Notably, the 100 mg/kg dose did not yield significant effects.

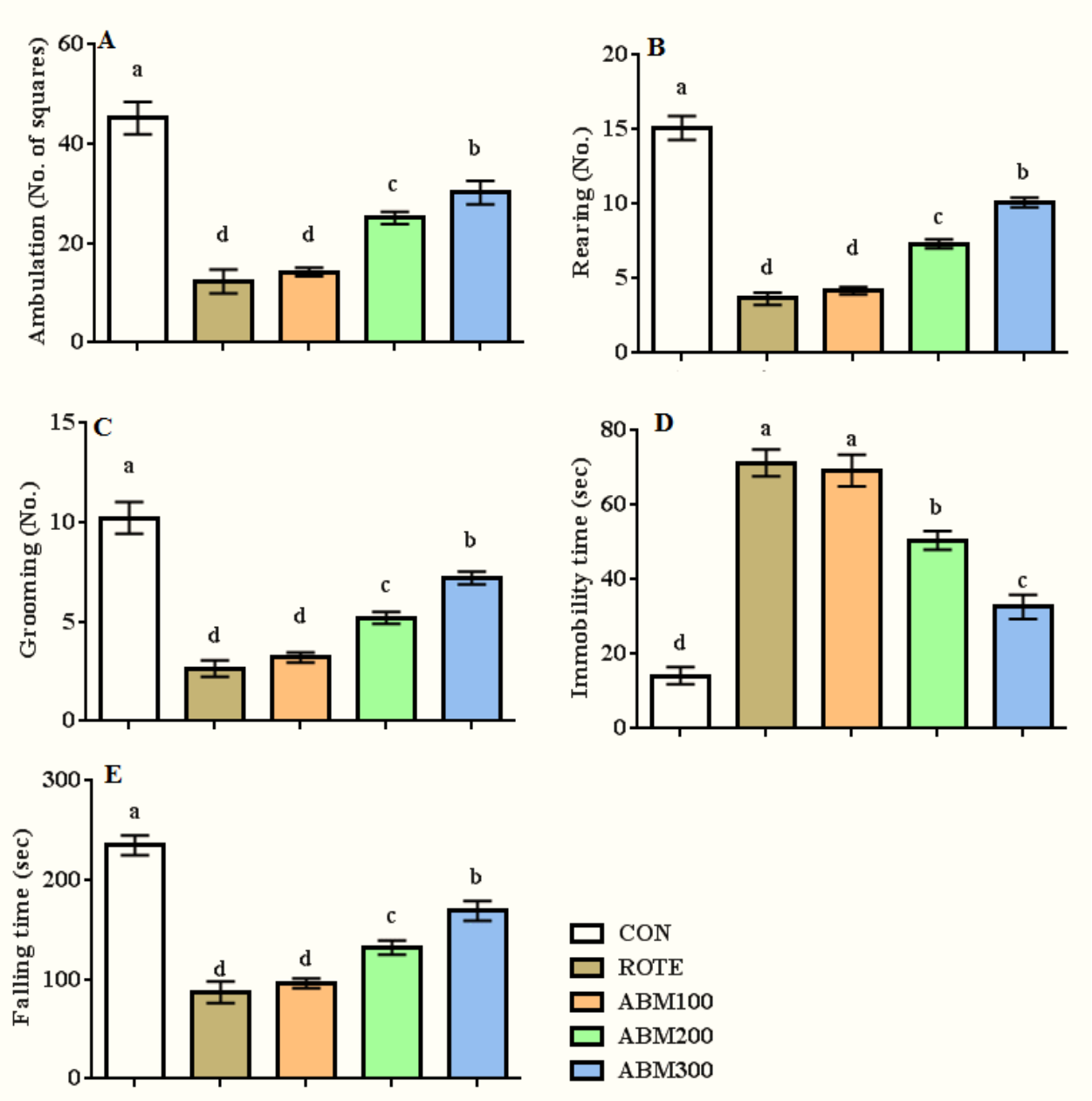


Figure 1. The effects of Agaricus bisporus mushroom on rotenone-induced alterations in motor activity and coordination in the open field and rotarod tests. Superscripts (a-d) show significant differences between groups. Control group (CON), ROTE: Rotenone, ABM 100, ABM 200 and ABM 300: received 100, 200 and 300 mg/kg of A. bisporus mushroom.

3.4. Antioxidant responses

Table 1 provides an overview of the study results, highlighting the effects of A. bisporus mushroom on striatal antioxidant responses. Rotenone administration led to a significant decrease in the activities of SOD,

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GSH, and CAT, accompanied by an increase in MDA compared to the control group (P=0.001). However, A. bisporus mushroom at doses of 200 mg/kg and 300 mg/kg demonstrated a significant increase in the activities of SOD, GSH, and CAT, coupled with a decrease in MDA compared to both the control and ROTE groups (P=0.001). Notably, the 100 mg/kg dose did not yield significant effects.

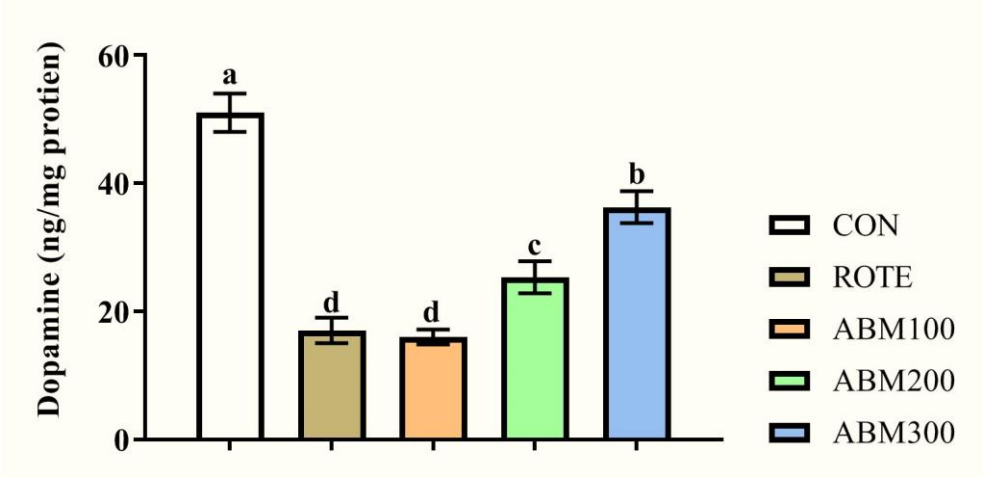


Figure 2. The effects of Agaricus bisporus mushroom on striatal dopamine content. Superscripts (a-d) show significant differences between groups. Control group (CON), ROTE: Rotenone, ABM 100, ABM 200 and ABM 300: received 100, 200 and 300 mg/kg of A. bisporus mushroom.

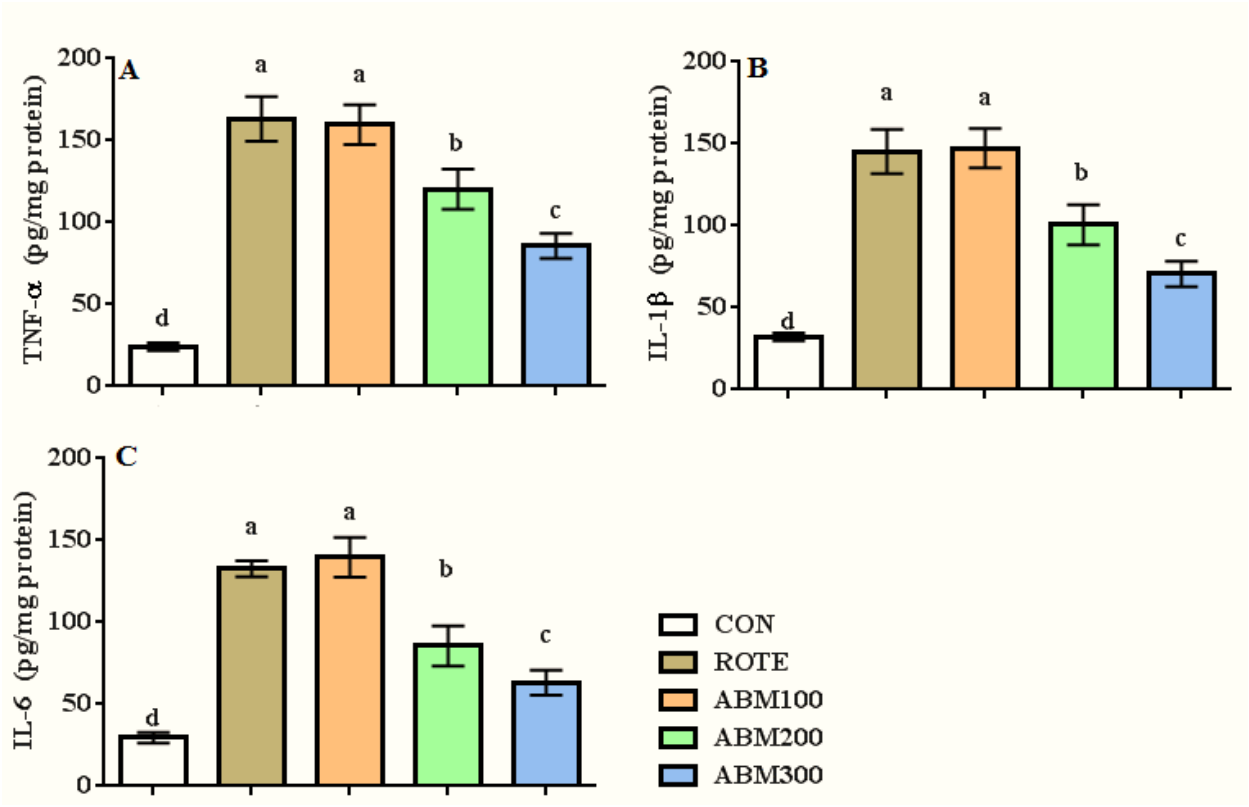


Figure 3. The effects of Agaricus bisporus mushroom on striatal pro-inflammatory cytokines. Superscripts (a-d) show significant differences between groups. Control group (CON), ROTE: Rotenone, ABM 100, ABM 200 and ABM 300: received 100, 200 and 300 mg/kg of A. bisporus mushroom.

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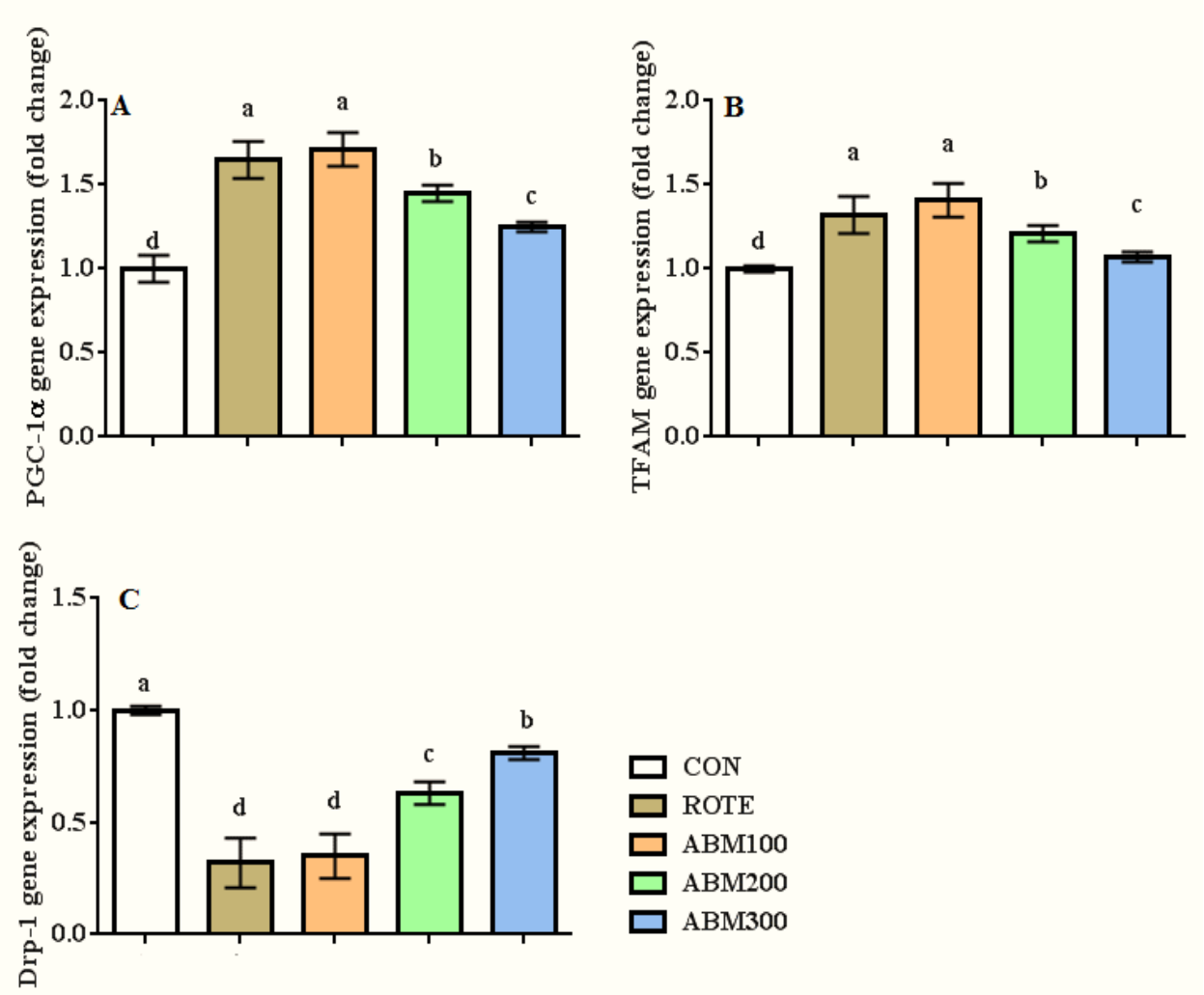
3.5. The expression of Drp-1, PGC1α and TFAM

Figure 4 presents the findings regarding the influence of A. bisporus mushroom on the expressions of Drp-1, PGC1α, and TFAM. Rotenone administration significantly decreased Drp-1 expression and increased PGC1α and TFAM expressions when compared to the control group (P=0.001). In contrast, A. bisporus mushroom at doses of 200 mg/kg and 300 mg/kg significantly increased Drp-1 expression and decreased PGC1α and TFAM expressions compared to the ROTE group (P=0.001). However, the 100 mg/kg dose did not yield significant effects.

Table 1. The effects of Agaricus bisporus mushroom on striatal antioxidant responses

Groups	MDA	SOD	GSH	CAT
CON	7.78±0.56^{d}	341.23±8.20^{a}	10.52±0.21^{a}	41.10±1.20^{a}
ROTE	45.23±1.23^{a}	156.23±8.45^{d}	0.78±0.41^{d}	6.32±0.45^{d}
ABM100	42.18±2.10^{a}	163.96±4.25^{d}	1.05±0.25^{d}	6.96±1.25^{d}
ABM200	36.51±2.33^{b}	197.32±14.33^{b}	3.63±0.53^{b}	17.12±1.33^{b}
ABM300	25.10±2.20^{c}	145.20±16.30^{c}	6.32±1.45^{c}	25.32±3.21^{c}
P-values	0.001	0.001	0.001	0.001

Superscripts (a-d) show significant differences between groups. Control group (CON), ROTE: Rotenone, ABM 100, ABM 200 and ABM 300: received 100, 200 and 300 mg/kg of A. bisporus mushroom.



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Figure 4. The effects of Agaricus bisporus mushroom on the expressions of Drp-1, PGC1α and TFAM. Superscripts (a-d) show significant differences between groups. Control group (CON), ROTE: Rotenone, ABM 100, ABM 200 and ABM 300: received 100, 200 and 300 mg/kg of A. bisporus mushroom.

4. Discussion

This study aimed to assess the neuroprotective effects of A. bisporus mushroom in a rotenone-induced rat model of Parkinson's disease. The results indicated that rotenone had detrimental effects on behavioral responses, consistent with previous studies [23-25]. These cognitive and behavioral symptoms, including depression, anxiety, and loss of interest, align with common manifestations of Parkinson's disease. In advanced stages, dementia can also occur [26], accompanied by sleep disturbances and sensory issues [27]. Rotenone's impact on behavioral responses may be linked to its inflammatory, oxidative, and dopaminergic effects, as discussed. Notably, A. bisporus mushroom demonstrated an improvement in behavioral responses, aligning with findings from other studies on mushroom effects [28, 29]. Furthermore, rotenone significantly reduced dopamine levels, corroborating existing research [30, 31]. In Parkinson's disease, the progressive loss of dopamine-producing neurons in the brain leads to symptoms like tremors, slowness, stiffness, and balance issues [32]. Dopamine, a crucial neurotransmitter, regulates various body functions, particularly movement and coordination [31]. Low dopamine levels result in movement problems, disrupting the nigrostriatal pathway between the substantia nigra and the striatum in the basal ganglia. Studies indicate that individuals with Parkinson's lose a substantial percentage of dopamine-producing cells in the substantia nigra [35, 36]. Interestingly, higher doses of A. bisporus mushroom were associated with increased dopamine levels, suggesting potential protective and antioxidant effects. However, the lack of positive effects at 100 mg/kg may be attributed to its lower concentration of active components. These findings underscore the potential of A. bisporus mushroom as a protective agent against Parkinson's disease, with dose-dependent effects on behavioral responses and dopamine levels. The results indicated that rotenone heightened inflammation and inflammatory responses, consistent with prior research [37, 38]. Numerous studies on patients with Parkinson's disease have reported alterations in inflammatory markers and immune cell populations in peripheral blood and cerebrospinal fluid. These changes may trigger or intensify neuroinflammation, perpetuating the neurodegenerative process [39, 40]. Several disease-related genes and risk factors are recognized as immune function modulators in Parkinson's disease. Growing evidence suggests the involvement of viral or bacterial exposures, pesticides, and alterations in gut microbiota in the disease's pathogenesis [41, 42]. Therefore, inflammation plays a substantial role in Parkinson's disease.

Conversely, the application of A. bisporus mushroom significantly decreased inflammation, aligning with findings from other studies [43, 44]. This suggests that A. bisporus mushroom possesses dose-dependent anti-inflammatory properties attributed to its specific compounds. In summary, rotenone exhibited pro-inflammatory effects, while the mushroom mitigated these effects, highlighting its potential as an anti-inflammatory agent in the context of Parkinson's disease. Rotenone induced a reduction in antioxidant enzymes' concentration and increased Malondialdehyde (MDA) content, consistent with previous studies exploring rotenone's impact on antioxidant responses in the context of Parkinson's disease [45, 46]. Oxidation plays a crucial role in disease progression, and measuring MDA levels, as a biomarker of oxidative stress, is pivotal for assessing the severity of oxidative damage. MDA, a highly reactive aldehyde compound, is generated through the peroxidation of unsaturated fatty acids. As an indicator of oxidative stress, MDA's reactivity extends to attacking other molecules, influencing their function, and ultimately impacting cellular function through the formation of strong covalent bonds [47, 48].

Catalase, an enzyme present in various living organisms, breaks down hydrogen peroxide into oxygen and water, contributing to the cellular defense against oxidative stress [49]. Superoxide dismutase (SOD) acts as an antioxidant and anti-inflammatory agent by neutralizing free radicals and preventing aging [50].

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Glutathione peroxidase, another vital enzyme, protects organisms from oxidative damage by reducing lipid hydroperoxides to corresponding alcohols and converting free hydrogen peroxide to water [51]. The observed decrease in antioxidant enzymes and the rise in MDA levels in the context of Parkinson's disease highlight the close relationship between the condition and oxidative stress. Conversely, A. bisporus mushroom exhibited antioxidant properties by significantly mitigating the decline in antioxidant enzymes. These results align with previous studies emphasizing the antioxidant potential of A. bisporus mushroom [52, 53]. The mushroom's ability to counteract oxidation could prove beneficial in alleviating the oxidative stress associated with Parkinson's disease. Furthermore, rotenone significantly altered the expression of Drp-1, PGC1α, and TFAM. Neurons rely on Drp-1 for axon maintenance and survival, while TFAM is closely associated with oxidative stress [22]. Therefore, these molecules play significant roles in reducing damage. The A. bisporus mushroom demonstrated the ability to significantly decrease the expression of these molecules, mitigating their negative effects. These findings underscore the potential neuroprotective effects of A. bisporus mushroom at the molecular level in the context of Parkinson's disease.

5. Conclusions

The outcomes of this study highlight the potential preventive effects of ABM200 and ABM300 against Parkinson's disease, particularly in relation to inflammation and oxidative stress. It is essential to note the study's limitation in being conducted on rats. However, the encouraging results provide a foundation for further investigations and warrant consideration in the ongoing exploration of preventive measures for Parkinson's disease.

Declarations

Author Contributions Statement:

Samira Rostami Mehr: Methodology; Formal analysis; Data curation; Writing-Original Draft. **Fatemeh Ghalami:** Methodology; Software; Formal analysis. **Saeid Abbasi-Maleki:** Writing and proofreading final draft; Data curation; Methodology; Analysis and interpretation of data. **Maryam Saada:** Investigation; Methodology; Writing-Review and Editing; Acquisition of data; Supervision; Project administration.

Conflicts of Interest:

The authors declare that they have no conflicts of interest.

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