RESEARCH ARTICLE

Anti-Parkinsonian Activity of Mushrooms Against Orofacial Dyskinesia Induced by Reserpine in Wistar Rats

Namrata Dargude[1*], Rupali Patil[2] and Chandrashekhar Upasani[1]

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Abstract

A neurological ailment called Parkinson's disease (PD) which distresses roughly 1.5% of people above age 65 in the world. Dopamine nerve cell death (DA) in the Substantia nigra parc compacta (SNc) with the development of a striatal DA deficiency are two features of PD.As of now, the focalization of PD is uncertain. The goal was to assess the neuroprotective efficacy of ethanolic extracts from different mushroom species viz. *P. ostreatus*, *A. bisporus* and *C. cibarius* are against orofacial dyskinesia (OD) by reserpine and their in vivo antioxidant status. In this study, reserpine (1-mg/kg) was repeatedly administered on alternate days over a five-day interval to produce vacuous chewing movements (VCMs) and tongue protrusions (TPs) in rats. Evaluation of reserpine-induced catalepsy was done. Catalase (CAT), glutathione reductase (GSH), superoxide dismutase (SOD) and lipid peroxidation (LPO) concentrations were examined in prosencephalon in response to an ethanolic extract of mushrooms. The histological evaluation of attenuating oxidative stress also shows the effectiveness of all these mushroom extracts. In animal models of Parkinson's disease produced by reserpine, *P. ostreatus, A. bisporus* and *C. cibarius* were found to have a therapeutic impact against the disease.

Keywords: Antioxidant, Anti-parkinsonian effect, Mushrooms, Orofacial dyskinesia, Tongue protrusions.

Highlights

- This research suggests that mushrooms can be useful for the therapy of Parkinson's syndrome.
- Phytochemical constituents present in the mushrooms and its antioxidant property was evaluated by using animal models.
- Provides the possible use of mushroom as dietary supplement and as a nutraceutical.
- Mushrooms can show a neuroprotective effect.

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Introduction

Parkinson's disorder (PD) is most commonly triggered the gradual and progressive loss of neural tissue and neurologic functional disorder whose onset increases with the progression of age. PD is characterized by tremors, rigidity, and slowness of movement, as well as symptoms including depression and insomnia (Javier Blesa *et al.,* 2014) and this progressed through the loss of dopamine nerve cells in the substantia nigra. James Parkinson originally described PD in 1817 as shaking palsy or "trembling paralysis" (Parkinson 2002, Gandhi 2005). Neurodegeneration is due to several mechanisms, such as suppression of the mitochondrial complex 1 (Schmidt, Alam 2006, Sherer*et al*., 2006), and environmental poisons like metals (Sherer, Betarbet 2002), which interact with genetic and environmental variables. Failure of the protocolar system (Tanner 1989, Hirsch *et al.,* 1991) and activation of the microglia (Mcnaught *et al.,* 2003, McGeer *et al.,* 1988, Hauss-Wegrzyniak *et al.,* 1998). These flaws may release free radicals that induce oxidative damage to the metabolism of dopamine (Lotharius, O'Malley 2000).This produces reactive oxygen species (ROS) (Chen *et al.,* 2008, Zoccarato, Toscano, 2005). Nitric oxide (NO) levels increased, and endogenous antioxidant molecules like glutathione (GSH) and superoxide dismutase (SOD) levels decreased. According to these specifications, antioxidants must be used in conjunction to other protective agents to treat PD (Sharmaa Neha, Ranaa 2011). The components of ongoing processes such as mitochondrial failure, excitotoxicity, nitric oxide toxicity, and inflammation are all directly related to oxidative stress (Nikam*et al.,* 2009). Since medications can only slow down the progression of neurodegenerative illnesses, there are currently no effective treatments and the disease progresses periodically. Mushrooms provide potent anti-inflammatory, anticancer, immune-modulating, antibacterial, hepatoprotective, antidiabetic, and vitamin-rich therapeutic activities (Uttara, Singh 2009). Mushrooms are a strong source of energy and antioxidants, reduce oxidative stress and can be used as nutritional supplements (I.C. Li *et al.,* 2018, Vendditti*et al.,* 2017). Mushrooms that can be consumed have potent nutraceutical benefits that may decrease the sequel of Alzheimer's disease (AD) and PD. Similar to Alzheimer's disease and Parkinson's Disease, the bioactive chemicals contained in mushrooms have an impact on the occurrence of other neurodegenerative disorders (NDs), such as Huntington's disease (HD), multiple sclerosis (MS) and motor neuron disease (MND) (Phan, David 2017, Phan, David2015). The mushroom shows it's anti-cataleptic

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action and antioxidant effect as a mark or indication of an anti-parkinsonian effect by reducing oxidative stress (Dugger, Dickson 2017). Since ancient time, mushrooms has been used as food and medicine (Bais, Gill Singh2014). Hence, this study sought to assess the impact of various mushrooms on the reserpine-induced OD model, a widely accepted pre-clinical model of PD.

Materials And Methods

Procurement of Plant and extraction process

Pleurotus ostreatus (PO) (*Pleurotaceae*), *Agaricus biosporus* (AB) (*Agaricaceae*), and *Cantharellus cibarius* (CC) (*Cantharellaceae*) mushrooms were bought from the local market. Dr. D. G. Shimpi, Botany Department, RNC Arts, JDB Commerce and NSC Science College, Nashik Road, Maharashtra, identified and verified the plant specimen. The Soxhlet extraction method was used to prepare the ethanolic extract.

Animals

Male Wistar rats (150–200 gm) were acclimatized to the lab environment. The institutional animal ethics committee of Sudhakarrao Naik Institute of Pharmacy, Pusad (729/PO/Re/S/11/CPCSEA) approved the experimental protocols, and the study was conducted in accordance with the standards of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), New Delhi, India.

Phytochemical Evaluation

The phytochemical analysis was performed to check the presence of alkaloids, flavonoids, terpenoids, steroids, glycosides and phenolic compounds from the selected species.

Drugs and Treatment Schedule

Reserpine was diluted with glacial acetic acid and extract was diluted with distilled water. The diluted extract was used for the oral administration to the rats. Animals were divided in twelve groups and extract, vehicle and reserpine (1-mg/kg, s.c. on alternate day) was administered for five days. Behavioral tests like vacuous chewing motions (VCM), orofacial bursts (OB) and tongue protrusions (TP) for all groups of animals was assessed and biochemical estimation was done on fifth day. All groups received the required treatment of an extract at a specified dose. All groups were treated with the selected doses as per the studies previously conducted literature are as follows; Group I Control], Group II [Reserpine (1-mg/kg, s.c)], Group III [Extract of *P. ostreatus* (50 mg/kg, p.o) + Reserpine (1-mg/kg, s.c)], Group IV [Extract of *P. ostreatus* (100 mg/kg, p.o) + Reserpine (1mg/kg, s.c)], Group V [Extract of *P. ostreatus* (250 mg/kg, p.o)+ Reserpine (1-mg/kg, s.c)],Group VI [Extract of *A. bisporus* (25mg/kg, p.o) + reserpine (1-mg/kg, s.c)], Group VII [Extract of *A. bisporus* (50mg/kg, p.o) + Reserpine (1-mg/kg, s.c)], Group VIII [Extract of *A. bisporus* (100 mg/kg, p.o) + Reserpine (1-mg/kg, s.c)], Group IX [Extract of *C. cibarius* (100 mg/kg, p.o) + Reserpine (1-mg/kg, s.c)], Group X [Extract of *C. cibarius* (200 mg/kg, p.o) + Reserpine (1mg/kg, s.c)], Group XI [Extract of *C. cibarius* (400 mg/kg, p.o) + Reserpine (1-mg/kg, s.c)], Group XII [Vit. E (10 mg/kg) + Reserpine (1-mg/kg, s.c)].

Evaluation of Biochemical Estimation

After the catalepsy was measured, animals were sacrificed. The forebrain dissection was done, rinsed with isotonic saline, weighed once the brains had been removed, and homogenization was done with 0.1N HCl. Post-nuclear fractions (10% (w/v) tissue homogenate) for catalase assay was prepared in 0.1M phosphate buffer (pH 7.4). The other enzyme assays were performed by centrifuging a homogenate at 1200 g for 60 minutes at 4°C. (Patil *et al.,* 2012)

Evaluation of Behavioral Parameters

Rats were kept in a plexiglass observation box (22 ×22×22 cm) for a habituation period of 10 minutes followed by reserpine injection. The rats were observed for five minutes and then VCMs, OBs and TPs were counted by an observer who is blind to the therapy. Locomotor activity was assessed using open-field equipment. The total number of covered fields traveled was counted for five minutes (Cousins and Carriero 1997).

Measurement of Superoxide Dismutase (SOD) Activity

Superoxide dismutase prevents oxidation of adrenaline to adrenochrome which works as the base for the evaluation of this study. The optical density was evaluated with reference to blank for the reagent at 480 nm and data was represented as milligrams per protein of SOD activity (Patil *et al.,* 2012). The method followed is 2.0 mL of carbonate buffer and 0.5 mL of EDTA were added to 0.05 mL of supernatant. The auto-oxidation of adrenaline (3×10^{-4} M) to adrenochrome at pH 10.2 was determined by monitoring changes in optical density at 480 nm. The reaction will be started by adding 0.5 mL of epinephrine. At 480 nm, the optical density variations per minute were observed in comparison to a reagent blank. The findings will be presented in milligrams per protein or units of SOD activity. Adrenaline was inhibited by 50% with one unit of SOD activity. The findings shall be presented in nmol SOD U per milligram of wet tissue and SOD activity will calculated by the below formula.

%inhibition = [(control XO rate − sample rate)/(control XO rate)] × 100.

Measurement of Catalase (CAT) Activity

Catalase assay was Beers and Sizer's (1952). Absorbance was measured at 240nm at an interval of 10 seconds for one minute. The data is represented as milligrams per protein of CAT activity (Patil *et al.,* 2012). The method consists of the reaction mixture of 2 mL phosphate buffer (pH 7.0), 0.95 mL of hydrogen peroxide (0.019 M), and 0.05 mL supernatant in final volume of 3 mL. Absorbance will be recorded at 240 nm every 10 seconds for 1-minute. One unit of CAT was defined as the amount of enzyme required to decompose 1 mmol of peroxide per minute at 25°C and pH 7.0. The results will be expressed as units of CAT activity (milligrams per protein). Units of activity will be determined from the standard graph of H2O2. The results will be expressed as catalase U per mg wet tissue and CAT activity calculated by formula below.

$k/mg = k_{total/ml}\ /mg/ml^{-1}$

Estimation of Reduced Glutathione

The homogenate was treated with 10% trichloroacetic acid and treated with 1.0mL of Ellman's reagent after centrifugation. The

reagent composed of 19.8 mL of 5, 5-O-dithiobisnitro benzoic acid dissolved in 100 mL of 1.0% sodium citrate and 3 mL of phosphate buffer (pH 8.0) absorbance was checked at 412 nm in form of nanomole GSH per milligram of wet tissue (Patil *et al.,* 2012). Reduced glutathione was calculated using the formula below.

GSH concentration = Total Glutathione – oxidized glutathione (GSSG)

Reduced glutathione concentration is calculated by subtracting oxidized glutathione concentration from total glutathione concentration

Estimation of Lipid Peroxidative Indices

The extent of peroxidation of lipid was determined by the generation of thiobarbiturate-reactive compounds (TBARS).The absorbance was calculated with reference to a blank at 535 nm (Patil *et al.,* 2012). The method consists of 0.1 mL of homogenate (Tris-HCl buffer, pH 7.5) was treated with 2 mL of (1: 1: 1 ratio) TBA-TCA-HCl reagent (thiobarbituric acid 0.37%, 0.25N HCl, and 15% TCA) and will be placed in water bath for 15 minutes for cooling, and centrifugation at room temperature for 10 minutes at 1000 g. The absorbance of clear supernatant will be measured against a reference blank at 535 nm. The results will be expressed as LPO nanomole per milligram wet tissue.

Dopamine Content in forebrain region of Rat

The entire brain was extracted and homogenized in butanol to estimate DA. Using the Cox and Perhach (1973) method, the levels of DA in the entire brain were calculated spectrophotofluorometrically (Verma 1993).

Statistical Analysis

One-way ANOVA with post-hoc Dunnett's test was used for statistical analysis by GraphPad Prism software of version 10. $p < 0.0001$ was found to be statistically significant.(*$p < 0.05$, ** $p < 0.001$, ***$p < 0.0001$, **** $p < 0.00001$). Analysis done by comparing treatment groups with group II which received reserpine (1-mg/kg, s.c).

Result And Disscussion

Phytochemical Screening of ethanolic extract of mushroom species

A phytochemical screening exposed the presence of tannins, alkaloids, flavonoids, glycosides and steroids in ethanolic extracts of all the three species of mushrooms.

Effect of mushroom on reserpine induced Catalepsy in Rats

TP, VCM and OB were all significantly ($p < 0.0001$) increased after receiving reserpine (1-mg/kg, s.c.) on alternate days for a period of 5 days. Treatment of vitamin E (10 mg/kg), extract of *A. bisporus* (25 mg/kg p.o), *P. ostreatus* (250 mg/kg p.o) and extract of *C. cibarius* (200 mg/kg p.o) remarkably and dose-dependently reduced reserpine-induced VCMs, TPs and OBs (as shown in Figs 1-3).

Five days of alternate-day reserpine administration resulted in a considerably ($p < 0.0001$) decreased locomotor activity. *A. bisporus* extract (25 mg/kg dose p.o.), *P. ostreatus* extract (250

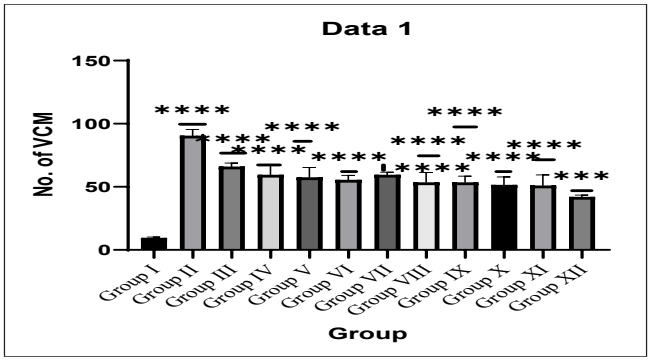


Fig. (1): Effect of *P. ostreatus, A. bisporus and C. cibarius* ethanolic extract on Reserpine-induced vacuous chewing movements (VCM), in rats. (**** $p < 0.0001$, *** $p < 0.001$,** $p < 0.01$)

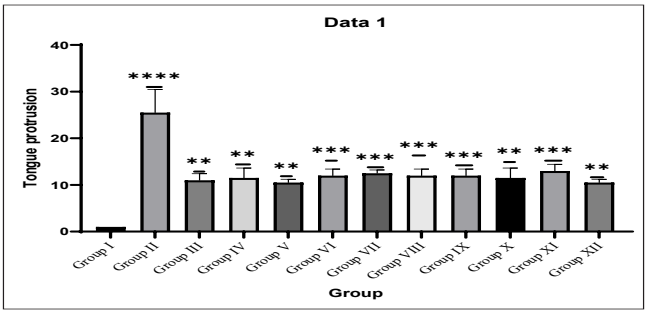


Fig. (2): Effect of *P. ostreatus, A. bisporus and C. cibarius*ethanolic extract on Reserpine-induced orofacial bursts (OB). (**** $p < 0.0001$, *** $p < 0.001$,** $p < 0.01$)

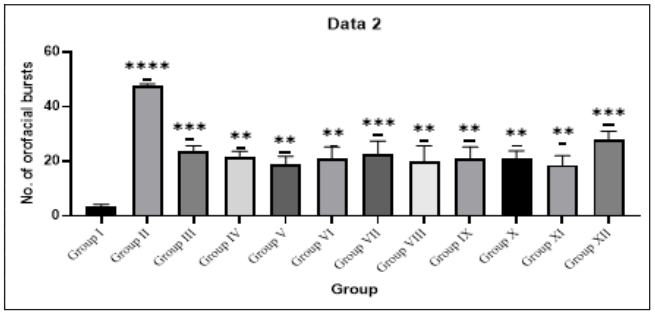


Fig. (3): Effect of *P. ostreatus, A. bisporus and C. cibarius*ethanolic extract on Reserpine-induced tongue protrusion (TP) in rats. (**** $p < 0.0001$, *** $p < 0.001$,** $p < 0.01$)

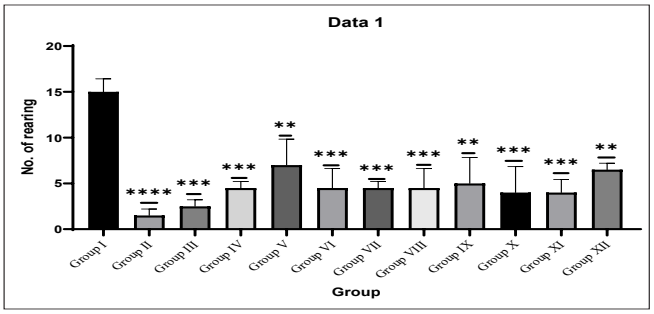


Fig. (4): Effect of *P. ostreatus, A. bisporus and C. cibarius* ethanolic extract on locomotor activity (number of rearing) in reserpine treated rats and no. of square transversed) (**** $p < 0.0001$, *** $p < 0.001$,** $p < 0.01$)

mg/kg dose po), *C. cibarius* extract (200 mg/kg dose p.o.) and vitamin E (10 mg/kg) pretreatment remarkably reduced effect of reserpine-induced locomotor activity as Vit. E attenuates the oxidative stress effect of reserpine observed in rats as shown in Figs 4 and 5. Histology of the brain tissue shows the protective changes in the thickness of purkinje fibers and granular cells after receiving the extract treatment (Fig. 6). effect of extract treatment on SOD, GSH, LPO and CAT levels represented in Table 1.

Reserpine-treated animals revealed an enhancement in the concentrations of lipid peroxidation and decreased levels of GSH, SOD and CAT, implying a possible free radicals creation. Treatment with all mushroom extracts and vitamin E (10 mg/kg) reduced these increased concentrations of lipid peroxidation. Additionally rise in concentrations of GSH and protective enzymes such as SOD and CAT, indicating its probable antioxidant action.

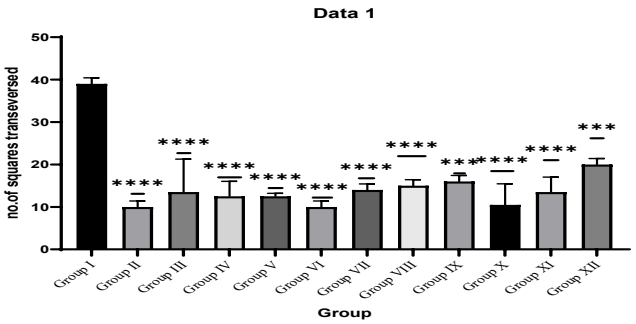


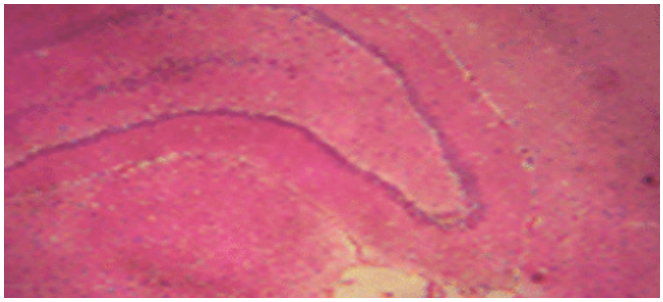
Fig. (5): Effect of *P. ostreatus, A. bisporus and C. cibarius*ethanolic extract on locomotor activity (number of square transversed) in reserpine treated rats. (**** $p < 0.0001$, *** $p < 0.001$,** $p < 0.01$)

A stooped posture, a trembling tremor and limb weakness most distinguish Parkinson's disorder. Clinically, bradykinesia, rigidity, trembling tremors, and postural unsteadiness are the four cardinal signs of this condition. Parkinsonism, which is characterized by the diminution of the neurotransmitter dopamine (DA) in the striatum, is the cause of these motor symptoms. Parkinson's disease is caused by the destruction of dopaminergic neurons in the Lewy bodies and substantia nigra pars compacta. Dopamine replacement therapy is the mainstay of current treatment for Parkinson's disease (PD) though it has long-term side effects, including dyskinesia (Xue Jiang, Siqi Li *et al.,* 2022). Plants with therapeutic benefits and a safer option to the treatment of Parkinsonism and other neurodegenerative conditions. Numerous animal models are available for the assessment of Parkinson's pharmacotherapeutics (Bais S, Naresh Singh Gill, 2014). Reserpine is used to create PD animal models in research. Parkinson's disease treatment studies have been conducted on mushroom extract. The current study aimed to determine the plant's anti-cataleptic activity as a sign or indication of its anti-Parkinson's action (Singh A,

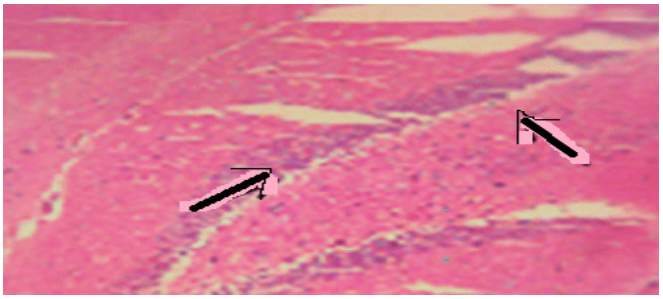
Table 1: Effect of ethanolic extract of *P. ostreatus*, *A. bisporus* and *C. cibarius* on reserpine induced orofacial dyskinesia in rats.

Group No.	*Group*	*Superoxide dismutase (SOD) Activity (U/milligram of wet tissue)*	*Catalase (CAT) activity (U/milligram of wet tissue)*	*Lipid peroxidation indices (LPO) (μM/ milligram of wet tissue)*	*Glutathione (GSH) levels (nmol/milligram of wet tissue*
Group I	Control	2.29 ± 0.05	7.85 ± 0.08	1.85 ± 0.04	13.96 ± 0.45
Group II	Reserpine (1 milligram/kilogram, s.c)	1.68 ± 0.01#	2.27 ± 0.07#	16.27 ± 0.36#	6.37 ± 0.05#
Group III	Extract of P. ostreatus (50 milligram/kilogram, p.o) + reserpine (1 mg/kg, s.c)	1.94 ± 0.05#	3.75 ± 0.12#	2.14 ± 0.78#	6.65 ± 0.06#
Group IV	Extract of P. ostreatus (100 milligram/kilogram, p.o) + reserpine (1 milligram/kilogram, s.c)	1.98 ± 0.04#	3.88 ± 0.09#	2.87 ± 0.98#	6.78 ± 0.09#
Group V	Extract of P. ostreatus (250 milligram/kilogram, p.o) + reserpine (1 milligram/kilogram, s.c)	1.99 ± 0.03****	3.97 ± 0.04****	3.43 ± 0.08****	6.93 ± 0.23****
Group VI	Extract of A. bisporus (25 milligram/kilogram, p.o) + Reserpine (1 milligram/kilogram, s.c)	2.01 ± 0.06****	4.57 ± 0.79****	3.96 ± 0.69****	7.23 ± 0.34****
Group VII	Extract of A. bisporus (50 milligram/kilogram, p.o) + Reserpine (1 milligram/kilogram, s.c)	2.09 ± 0.58*	4.68 ± 0.04*	4.12 ± 0.32*	7.43 ± 0.67*
Group VIII	Extract of A. bisporus (100 milligram/kilogram, p.o) + Reserpine (1 milligram/kilogram, s.c)	2.12 ± 0.93****	4.75 ± 0.06****	4.67 ± 0.9****	7.86 ± 036****
Group IX	Extract of C. cibarius (100 milligram/kilogram, p.o) + Reserpine (1 milligram/kilogram, s.c)	2.15 ± 0.67****	4.87 ± 0.14****	4.89 ± 0.46****	7.98 ± 0.68****
Group X	Extract of C. cibarius (200 milligram/kg dose p.o) + Reserpine (1 milligram/kilogram, s.c)	2.19 ± 0.07****	4.89 ± 0.08****	5.34 ± 0.87****	8.23 ±0.79****
Group XI	Extract of C. cibarius (400 milligram/kilogram, p.o) + Reserpine (1 milligram/kilogram, s.c)	2.26 ± 0.07****	4.92 ± 0.05****	5.73 ± 0.12****	8.46 ± 0.57
Group XII	Vit. E (10 milligram/kilogram) + Reserpine (1 milligram/kilogram, s.c)	1.91 ± 0.04****	4.28 ± 0.03****	5.74 ± 0.05****	13.54 ± 0.06****

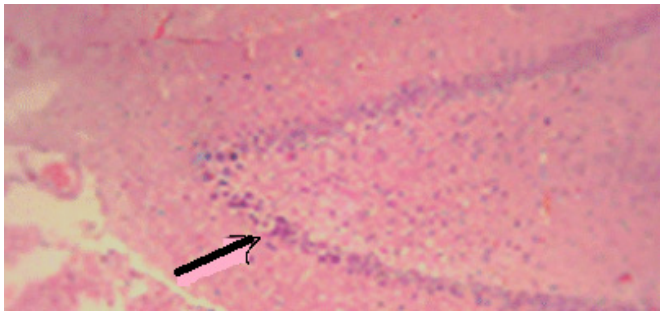
The observations are mean ± SEM ($n = 6$). #P <0.05 compared to control, *P <0.05 compared to reserpine (RE) treated group (one-way ANOVA followed by Dunnett's test).



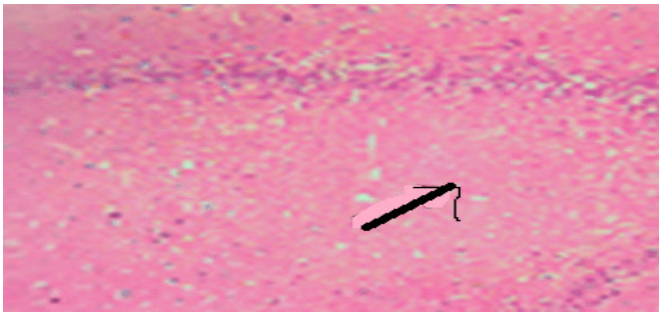
a) Normal Control rats



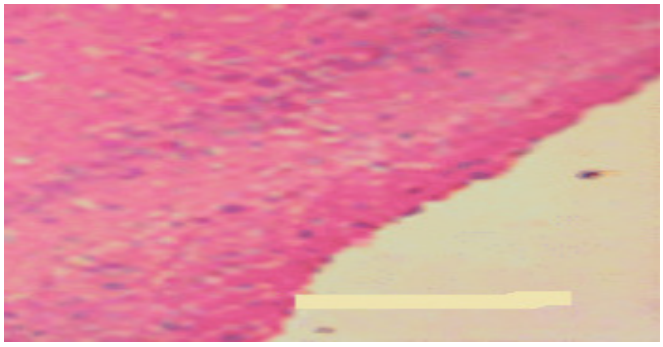
b) Rats treated with Reserpine (1milligram/kilogram, s.c)



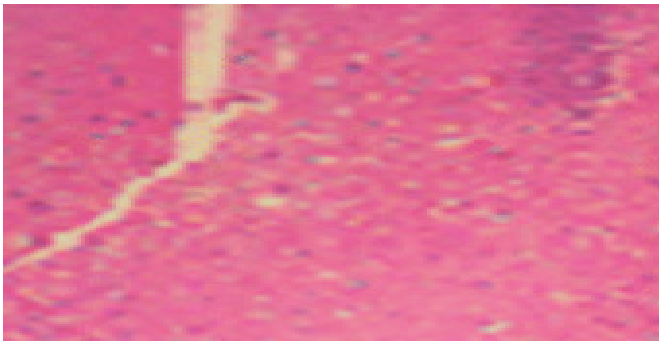
c) Rat treated with Extract of *P. ostreatus* (50 milligram/kilogram, p.o) + Reserpine (1 milligram/kilogram, s.c)



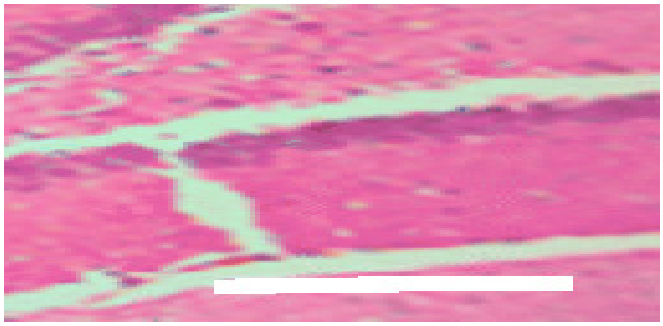
d) Rat treated with Extract of *P. ostreatus* (100 milligram/kilogram, p.o) + Reserpine (1 milligram/kilogram, s.c)



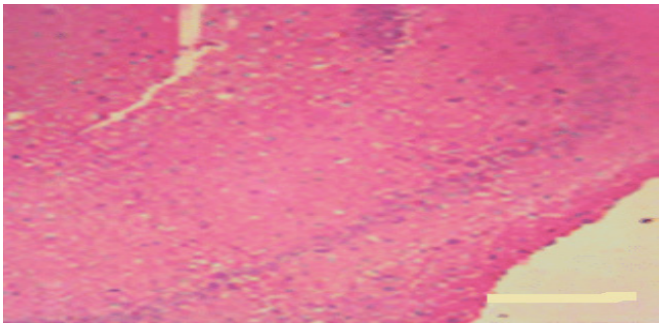
e) Rat treated with Extract of *P. ostreatus* (250 milligram/kilogram, p.o)+ Reserpine (1 milligram/kilogram, s.c)



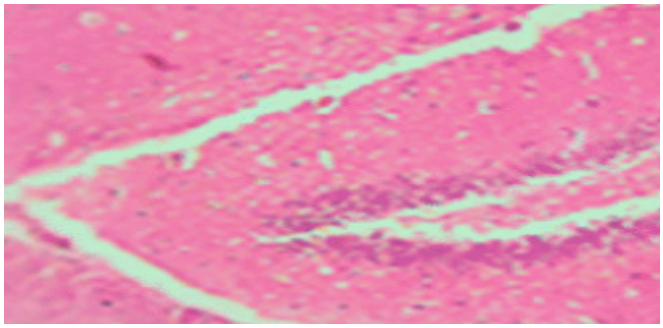
f) Rat treated with Extract of *A. bisporus* (25 milligram/kilogram, p.o) + Reserpine (1 milligram/kilogram s.c)



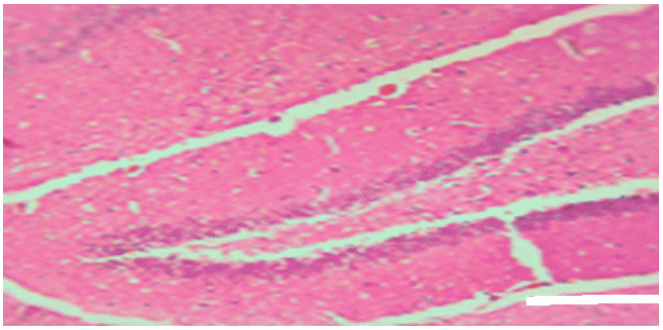
g) Rat treated with Extract of *A. bisporus* (50 milligram/kilogram, p.o) + Reserpine (1 milligram/kilogram, s.c)



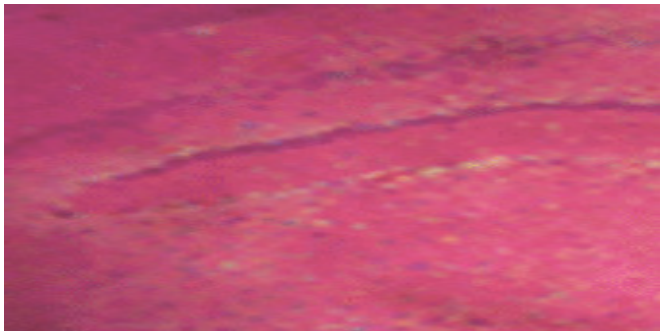
h) Rat treated with Extract of *A. bisporus* (100 milligram/kilogram, p.o) + Reserpine (1 milligram/kilogram, s.c)



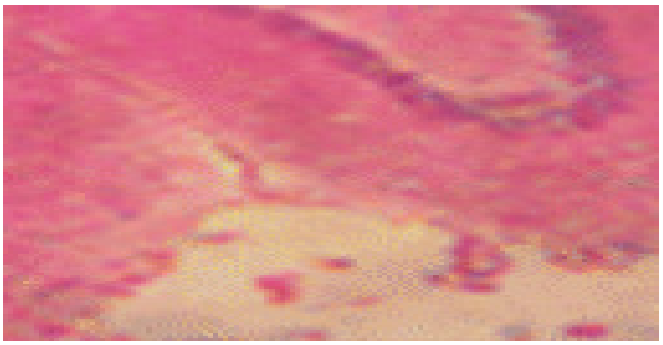
i) Rat treated with Vit.E (10 milligram/kilogram)+ Reserpine (1 milligram/kilogram, s.c)



j) Rat treated with Extract of *C. cibarius* (200 milligram/kilogram, p.o) + Reserpine (1 milligram/kilogram, s.c)



k) Rat treated with Extract of *C. cibarius* (400 milligram/kilogram dose p.o) + Reserpine (1 milligram/kilogram, s.c)



l) Rat treated with Vit. E (10 milligram/kilogram) + Reserpine (1 milligram/kilogram, s.c)

Fig. 6: The histological observation on the brain tissue of normal and experimental rats

Naidu P S, 2003).A typical animal study of Parkinson's disease is reserpine-induced orofacial dyskinesia. Failure to maintain facial expressions is referred to as orofacial dyskinesia. Reserpine causes the depletion of monoamines (5- hydroxytryptamine, norepinephrine and dopamine) in nerve endings, which leads to Parkinsonism. Reserpine interferes with the storage of catecholamines within intracellular granules. In comparison to the control group of rats, reserpine administered 1-mg/kg significantly increased VCM, OBs and TP in the rats, causing substantial orofacial dyskinesia. The mushroom extract had a dose-dependent impact on the orofacial dyskinesia that was reserpine-induced in rats. The protective effect of various mushroom species at doses between 50 and 400 mg/kg against reserpine-induced orofacial dyskinesia revealed that mushroom extract may have an impact on the treatment of Parkinson's disease (PD) (Yadav *et al.,* 2020).

In the present study, decreased level of SOD, GSH, CAT and increased levels of LPO resulted in free radical synthesis. The treatment with the reserpine is responsible for the increased levels of lipid peroxidation and decreased SOD, GSH, CAT, which represents the antioxidant activity of mushrooms. (Patil *et al.,* 2012, Sana Aslam *et al.,* 2021, Alvaro *et al.,* 2021). Mushrooms also contain tannins, alkaloids, flavonoids, glycosides, and steroids. The presence of the flavonoids suggests antioxidant activity. Biochemical studies showed that continuous reserpine treatment results suggest that the mushroom extracts possess antioxidant properties that can be used to counter the oxidative stress caused by chronic reserpine treatment. These findings provide support for the potential use of mushrooms as a natural remedy for oxidative stress-related diseases of the brain. Thus, this study concluded that oxidative stress could play an important role in the pathophysiology of reserpine-induced orofacial dyskinesia (Table 1).

Conclusion

In reserpine-induced animal PD models, *P. ostreatus, A. bisporus* and *C. cibarius* were revealed to have a therapeutic impact against Parkinson's disease. Due to the presence of flavonoids, they show antioxidant activity and are responsible for generating free radicals. For this impact to be applicable in treating Parkinson's disease in humans, clinical investigations are also required.

Author Contributions

Preparing, reviewing, and editing the research article's initial draft. All authors have read and agreed to the published version of the manuscript.

Conflict Of Interest

The authors have declared that no competing interests exist.

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