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Antidepressant-like activity of hydroalcoholic extract of *Agaricus blazei* in stressed and unstressed mice

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Abstract

The aim of this study was to investigate the antidepressant activity of hydroalcoholic extract *Agaricus blazei* (273 and 819 mg/kg; orally) in stressed and unstressed Swiss albino mice. Mice were immobilized to induce stress. Fluoxetine 20 mg/kg orally was given to stressed and unstressed animals and immobility time was noted by using forced swim test and tail suspension test. The concentration of plasma nitrite was also evaluated in stressed and unstressed mice. The effect of prazosin (α_1-adrenoceptor antagonist), p-CPA (parachlorophenylalanine–tryptophan hydroxylase inhibitor) and 7-nitro-indazole (nNOS inhibitor) on the antidepressant activity of *A. blazei* was also evaluated. *A. blazei* and fluoxetine significantly decreased the duration of immobility time in stressed and unstressed mice, showing significant antidepressant activity. No substantial change was found in the locomotor activity. However, a significant reduction in the level of plasma nitrite was also noted in stressed mice. Hydroalcoholic extract showed prominent antidepressant activity in mice.

Introduction

Depression is a widespread disorder in almost all the communities of the world which renders the person unable to perform the routine functions of life associated with one's professional and social life.

In clinical practice, many classes of drugs are used as antidepressant drugs which include specific serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, selective reversible inhibitors of monoamine oxidase A and selective serotonin reuptake inhibitors. But almost all these classes of drugs have numerous adverse drug reactions such as dizziness, confusion, insomnia, dry mouth, constipation, tachycardia, profuse sweating, weight changes and sexual dysfunction (Fajemiroye et al., 2016; Fava, 2003; Bet et al., 2013). This condition creates the need for the use of medicinal plants or plant-based medications for the treatment of depression.

St. John's wort, *Hypericum perforatum*, is a familiar plant for its clinical use to treat depression (Greeson et al., 2001). Other plants which possess antidepressant potential are *Echium amoenum* (Faryadian et al., 2014; Sayyah et al., 2006), *C. sativus* (Shafiee et al., 201; Lopresti and Drummond, 2014), *Lavandula spp.* (Kageyama et al., 2012; Rahmati et al., 2017), grape seed (Rabiei et al., 2017); *Hamelia patens* (Surana and Wagh, 2017), *Panax ginseng* (Dang et al., 2009; Ge et al., 2017), *Albizia julibrissin* (Kim et al., 2007; Liu et al., 2015), *Mentha pulegium* (Rabiei et al., 2016), *R. rosea* (Saki et al., 2014; Mao, 2014).

A medicinal mushroom called *Agaricus blazei* Murrill is recognized by different names in different countries. At present, it is extensively used in oriental countries not only as a valuable food but also as a potential natural

medicine in extract form (Giavasis, 2014). In this study, the antidepressant effect of the herb has been evaluated.

Materials and Methods

Drugs and chemicals

A. blazei extract was procured from ORIVeDA, ORIGO Holding BV, Amsterdam, The Netherlands. Fluoxetine was purchased from Hilton Pharma, Pakistan. Prazosin was bought from Pfizer, Pakistan. All other chemicals were purchased from Sigma-Aldrich, USA.

Animals

Male Swiss albino mice weighing 20–25 g and 3 months old were procured from the Karachi University. All the experimental mice were segregated into groups such that each polypropylene cage (approximately 29 × 22 × 14 cm) contained 6 mice and were facilitated by alternate light and dark cycle of 12 hours at a room temperature of (25-30°C). Free access to foodstuff and water were provided to the animals. However, food and water were not given to animals for 2 hours before and after the drug administration. Before conducting the experiments, an acclimatization period of 5 days was provided to animals.

Selection of doses

The dose selection of drugs and extract was done in accordance to the previous studies (Ni et al., 2013; Kwon et al., 2010; Binfaré et al., 2009; Rodrigues et al., 2002; Gilhotra et al., 2010).

Animal groups

Experimental design for assessing the antidepressant-like activity and nitrergic mechanism of *A. blazei* in unstressed and stressed mice using the tail suspension test: Group 1: Saline 10 mL/kg, *p.o.;* Group 2: Extract 273 mg/kg, *p.o.;* Group 3: Extract 819 mg/kg, *p.o.;* Group 4: fluoxetine 20 mg/kg, *p.o.;* Group 5: saline 10 mL/kg, *p.o.*+ 7-nitroindazole 20 mg/kg *i.p.;* Group 6: Extract 819 mg/kg, *p.o.*+7-nitroindazole 20 mg/kg *i.p.;* Group 7: saline 10 mL/kg, *p.o.* + stress; Group 8: Extract 273 mg/kg, *p.o.* + stress; Group 9: Extract 819 mg/kg, *p.o.*+ stress; Group 10: fluoxetine 20 mg/kg, *p.o.* + stress; Group 11: saline 10 mL/kg, *p.o.* + aminoguanidine 50 mg/kg *i.p.* + stress; Group 12: extract 819 mg/kg, *p.o.*+ aminoguanidine 50 mg/kg *i.p.* + stress.

Experimental design for assessing the antidepressant-like activity and nitrergic mechanism of *A. blazei* in unstressed and stressed mice using forced swim test: Group 13: Saline 10 mL/kg, *p.o.;* Group 14: Extract 273 mg/kg, *p.o.;* Group 15: Extract 819 mg/kg, *p.o.;* Group 16: Fluoxetine 20 mg/kg, *p.o.;* Group 17: Saline 10 mL/kg, *p.o.*+ 7-nitroindazole 20 mg/kg *i.p.;* Group 18: Extract 819 mg/kg, *p.o.*+ 7-nitroindazole 20 mg/kg *i.p.;* Group 19: Saline 10 mL/kg, *p.o.*+ stress; Group 20: Extract 273 mg/kg, *p.o.*+ stress; Group 21: Extract 819 mg/kg, *p.o.*+ stress; Group 22: Fluoxetine 20 mg/kg, *p.o.*+ stress; Group 23: Saline 10 mL/kg, *p.o.*+ aminoguanidine 50 mg/kg *i.p.*+ stress; Group 24: Extract 819 mg/kg, *p.o.*+ aminoguanidine 50 mg/kg *i.p.*+ stress.

Experimental design for assessing the monoaminergic mechanisms of the antidepressant-like activity of *A. blazei* in unstressed and stressed mice using tail suspension test. Group 25: Saline 10 mL/kg, *p.o.*+ sulpiride 50 mg/kg *i.p.;* Group 26: Extract 819 mg/kg, *p.o.*+ sulpiride 50 mg/kg *i.p.;* Group 27: Saline 10 mL/kg, *p.o.*+ prazosin 62.5 µg/kg *i.p.;* Group 28: Extract 819 mg/kg, *p.o.*+ prazosin 62.5 µg/kg *i.p.;* Group 29: Saline 10 mL/kg, *p.o.*+ p-CPA 100 mg/kg *i.p.;* Group 30: Extract 819 mg/kg, *p.o.*+ p-CPA 100 mg/kg *i.p.;* Group 31: Saline 10 mL/kg, *p.o.*+ sulpiride 50 mg/kg *i.p.*+ stress; Group 32: Extract 819 mg/kg, *p.o.*+ sulpiride 50 mg/kg *i.p.*+ stress; Group 33: Saline 10 mL/kg, *p.o.*+ prazosin 62.5 µg/kg *i.p.*+ stress; Group 34: Extract 819 mg/kg, *p.o.*+ prazosin 62.5 µg/kg *i.p.*+ stress; Group 35: Saline 10 mL/kg, *p.o.*+ p-CPA 100 mg/kg *i.p.*+ stress; Group 36: Extract 819 mg/kg, *p.o.*+ p-CPA 100 mg/kg *i.p.*+ stress.

Behavioral assessment

Induction of stress in mice

For stress induction, the mice were subjected to immobilization from 11 am to 1:30 pm (150 min) by positioning their backs on a wooden board by means of tape to stick all four limbs and trunk (Sheikh et al., 2007). The drugs were given 45 min before immobilization. The behavioral study was performed after 10 min of recovering the animal from the immobilization (Gilhotra et al., 2010).

Tail suspension test

This is the most important test to determine the antidepressant activity in mice. Each mouse was suspended individually by its tail at a height of 50 cm above the floor of the table edge with the aid of adhesive tape at about 1 cm from the tip of the tail. Whereas, the animal was separated both visually and acoustically from each other during the test. Immobility time was noted manually with the help of stopwatch for 6 min. If the animals did not exhibit any body movements, hung inertly and totally stationary, they were considered as immobile (da Silva et al., 2000).

Open-field test

For determination of the influence of *A. blazei* on locomotor activity, mice were assessed in the open-field model (TRU SCAN activity monitoring systems, Coulbourn Instruments) (Rodrigues et al., 1996). Individually the mice were placed in the center of the box (40 × 60 × 50 cm) to observe their behavior immediately and continues for 4 min. The compulsory factors/ parameters including total activities, entire distance and

Box 1: Forced Swim Test

Principle

The forced swim test (Porsolt test) is utilized for the evaluation of the antidepressant-like effects of the medication. The parameter noted in this test is called 'immobility', looking like a social condition of wretchedness, as found in human depression. In this test, mouse is compelled to swim in a limited space from which the mouse can't escape and is initiated to conduct of immobility. This conduct shows a condition of sadness which can be lessened with the use of antidepressant drug.

Requirements

Mouse, Stop watch, Swimming tank (transparent plexiglass, width 20 cm, stature 30 cm), Thermometer, Tissue roll

Procedure

Step 1: Fill the tank to the dimension of 15 cm

Step 2: Change the water temperature to 25 ± 1°C utilizing high temp water as well as ice to alter the temperature

Step 3: Note the temperature, utilizing a thermometer, before beginning the test

Step 4: Delicately and gradually pick the animal by the tail and move it into the swimming tank

Step 5: Begin the clock effectively set at 6 min

Step 6: After 6 min. expel the mouse from the swimming tank. Make it dry with a tissue, before exchanging it to its home cage.

Notes

Note down the mobility time for last 4 min (240 sec) of the total 6 min (360 sec) trial. Amid the underlying 2 min of total 6 min trial the mouse become incredibly active, vigorously, swim in circles, and endeavor to climb the divider or bounce to the base

Compute immobility time by subtracting portability time from the total time

Immobility = 240 sec - Mobility

References

Abel and Bilitzke, 1990; Can et al., 2012; Porsolt et al., 1977; Yu et al., 2002

References for videos

Rabiei et al., 2017; Rabiei et al., 2016

total ambulatory period were recorded with the help of a camera and protected in the computer (Liao et al., 2013).

Biochemical assessment

Determination of plasma nitrite

The plasma was obtained and centrifuged at 4°C for 10 min at 2,500 rpm. The plasma was refrigerated and then further processed for nitrite approximation within 24 hours (Dhingra and Bhankher, 2014). Spectrophotometric analysis based on Griess response was used for plasma nitrite estimation. In this reaction, plasma and Griess reagent were added in equal volume and incubated for 10 min at room temperature to obtain a chromophore. Spectrophotometer UV-VIS-NIR was used for the recorded absorbance at 543 nm. A standard curve was created to calculate nitrite concentration consuming sodium nitrite as standard and expressing the concentration of nitrite in micromoles (Green et al., 1982).

Statistical analysis

The data are shown as the mean ± standard error of the mean (SEM) with confidence intervals (CI) of 95%. The data are interpreted by using one-way ANOVA following Tukey's *post hoc* test. A probability level of 0.05 or less is accepted as significant.

Results

The mouse subjected to immobility stress for 150 min showed a significant increase (from 166.6 ± 4.4 sec to 198.0 ± 3.1 sec using tail suspension test; 159.2 ± 10.2 sec to 200.4 ± 13.1 sec using forced swim test) in the immobility time. These suggested depression-like behavior. The immobility time in both unstressed and stressed mice was significantly decreased (from 166.6 ± 4.4 sec to 141.2 ± 3.0 sec in unstressed mice and 198.0 ± 3.1 sec to 148.0 ± 3.1 sec in stressed mice using tail suspension test) by treatment with *A. blazei*. The results showed that the extract possesses significant antidepressant activity. The immobility period of unstressed mice treated with 7-nitroindazole (20 mg/kg) decreased when compared with the vehicle-treated unstressed mice. Aminoguanidine also increased the antidepressant effect of the mice pretreated with *A. blazei*. However, 7-nitroindazole did not potentiate the effect of unstressed mice pretreated with the extract (Figure 1). In the forced swim test, *A. blazei* significantly decreased the immobility time in both unstressed and stressed mice (Figure 1).

Immobilized animals showed a significant decrease in locomotor activity. The locomotor activity was decreased to 287.6 ± 9.6 sec when compared with the vehicle-treated group having the locomotor activity of 336.8 ± 7.3 sec. However, *A. blazei*, aminoguanidine, 7-nitroindazole and the combinations of the drugs did not produce any effect on the locomotor activity of unstressed and stressed mice when compared to their respective control groups (Figure 1).

The immobility time was significantly increased in prazosin, sulpiride and p-CPA groups when compared to their respective control groups. The change in immobility time was 202.2 ± 7.3 sec increased to 212.2 ± 4.9 sec for prazosin, 188.4 ± 4.9 sec increased to 212.0 ± 4.8 sec for sulpiride and 190.4 ± 7.7 sec increased to

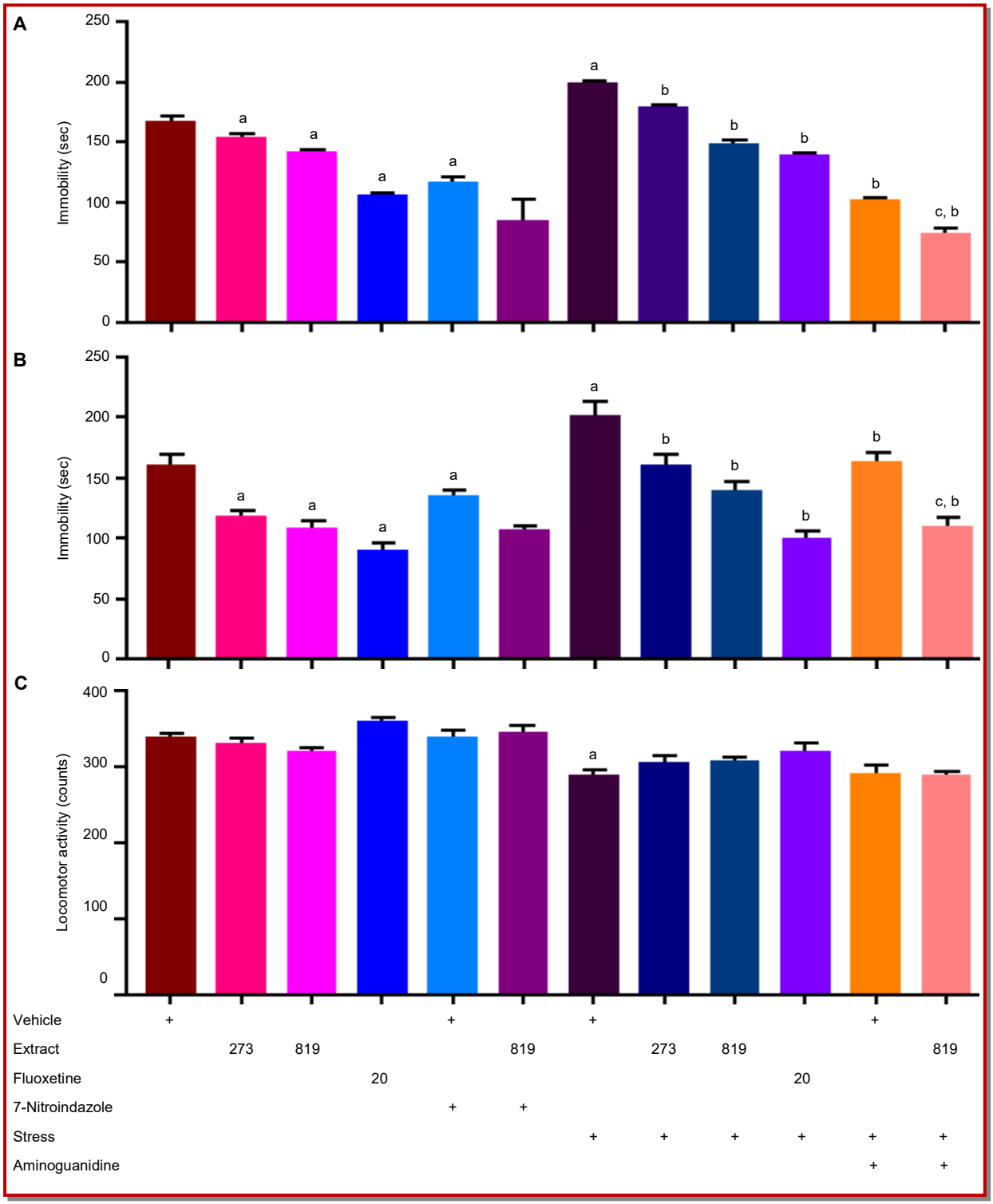

Figure 1: Effect of *A. blazei* and its combinations with 7-nitroindazole and aminoguanidine on immobility periods [using tail suspension test (A) and forced swim test (B)] and locomotor activity (C) of unstressed and stressed mice

n=6 in each group; Values are expressed as the mean ± SEM; Data were analyzed by one-way ANOVA followed by Tukey's test, except data for unstressed and stressed mice, which were analyzed by Student's unpaired t-test. [a]p<0.05, significant difference from vehicle-treated unstressed mice); [b]p<0.05, significant difference from immobilization-induced stressed mice; [c]p<0.05, significant difference from *A. blazei* (819 mg/kg)-treated stressed mice; [d]p<0.05, significant difference from aminoguanidine-treated stressed mice

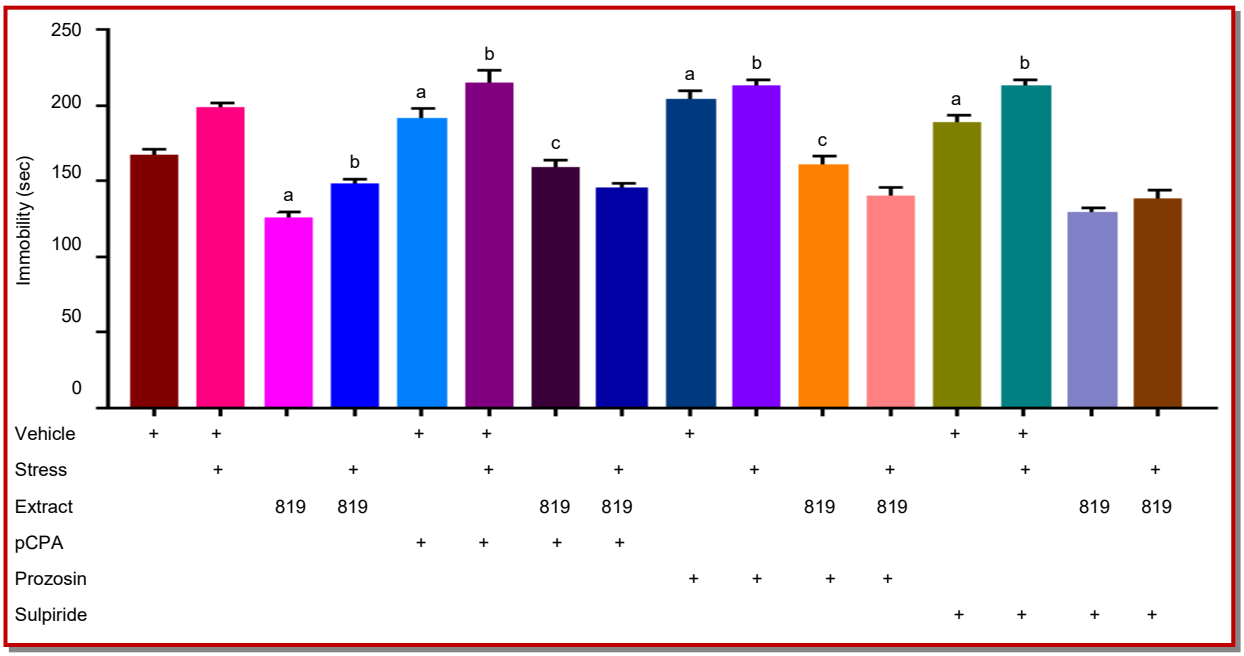

Figure 2: Effect of pCPA, prazosin and sulpiride *per se* and their combination with *A. blazei* on immobility periods of unstressed and stressed mice in TST.

n=6 in each group. Values are expressed as the mean ± SEM. Data were analyzed by one-way ANOVA followed by Tukey's test, except data for unstressed and stressed mice, which were analysed by Student's unpaired t-test. [a]p<0.05, significant difference from vehicle-treated unstressed mice); [b]p<0.05, significant difference from immobilization-induced stressed mice; [c]p<0.05, significant difference from *A. blazei* (819 mg/kg)-treated stressed mice; [d]p<0.05, significant difference from aminoguanidine-treated stressed mice

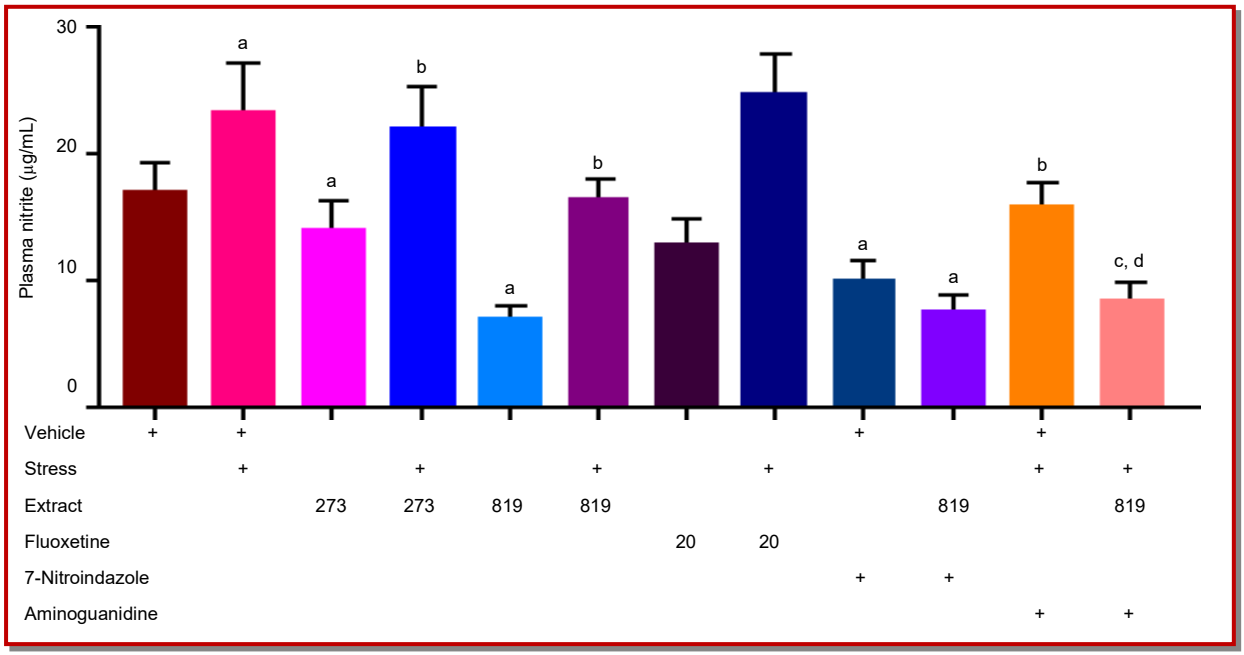

Figure 3: Effect of *A. blazei* and its combinations with 7-nitroindazole and aminoguanidine on plasma nitrite levels of unstressed and stressed mice.

n=6 in each group. Values are expressed as the mean ± SEM. Data were analyzed by one-way ANOVA followed by Tukey's test, except data for unstressed and stressed mice, which were analysed by Student's unpaired t-test. [a]p<0.05, significant difference from vehicle-treated unstressed mice); [b]p<0.05, significant difference from immobilization-induced stressed mice; [c]p<0.05, significant difference from *A. blazei* (819 mg/kg)-treated stressed mice; [d]p<0.05, significant difference from aminoguanidine-treated stressed mice

213.6 ± 9.7 sec for p-CPA.

However, pretreatment of the mice with prazosin and p -CPA reversed the decrease in immobility time produced by *A. blazei*. The change in immobility time was 148.0 ± 3.1 sec increased to 160.4 ± 6.4 sec by prazosin and 148.0 ± 3.1 sec increased to 158.6 ± 5.3 sec by p-CPA (Figure 2).

The plasma nitrite levels of stressed mice were elevated to 23.2 ± 3.9 µg/mL when compared with the vehicle-treated unstressed mice having the levels of 17.0 ± 2.2 µg/mL. The plasma nitrite levels of the stressed mice treated with the extract at the dose of 273 mg/kg and 819 mg/kg were significantly reduced to 14.0 ± 2.2 µg/mL and 7.0 ± 0.9 µg/mL respectively. There was also a significant decrease in the plasma nitrite levels in 7-nitroindazole and aminoguanidine groups. The change in plasma nitrite levels was 10.0 ± 1.5 µg/mL for 7-nitroindazole group and 15.8 ± 1.9 µg/mL for aminoguanidine group when compared to vehicle-treated control group having the levels of 23.2 ± 3.9 µg/mL.

The results also show that the plasma nitrite decreasing effect of the extract was significantly potentiated by aminoguanidine in stressed mice to the levels of 8.4 ± 1.4 µg/mL. However, 7-nitroindazole did not potentiate the plasma nitrite decreasing effect of the extract (Figure 3).

Discussion

The present study has demonstrated that *A. blazei* (273 mg/kg and 819 mg/kg, *p.o*) possesses the antidepressant-like effect in unstressed and stressed mice. This effect was assessed by utilizing the forced swim test and tail suspension test. These models are comprehensively used in rodents to foresee antidepressant-like potential by assessing the decrease in immobility time (Rodrigues et al., 2002)

Among the two doses of the extract, the dose of 819 mg/kg. *p.o.* showed the highest antidepressant-like activity in unstressed and stressed mice, so this dose of *A. blazei* was used to evaluate the mechanism of antidepressant activity. According to amine hypothesis, the depression is caused by the decreased concentration of serotonin (5-HT) and/or noradrenaline (NA) in the brain. This speculation is bolstered by the way that the depression is mitigated using the drugs that elevate the levels of amine neurotransmitters (Krishnan and Nestler, 2008). Practically all antidepressant medications act upon one or more of the following mechanisms to give their effect: hindrance of 5-HT reuptake or NA (and DA), restraint of monoamine oxidase or threat of inhibitory preganglionic NA or 5-HT receptors. These components result in the expanded neurotransmission of NA and additionally 5-HT. The findings of this study show that the antidepressant-like effect of *A. blazei* in unstressed mice was reversed by pretreatment with prazosin and p-CPA. As p-CPA is a serotonin synthesis inhibitor so for serotonin deletion p-CPA was given for four consecutive days (Binfaré et al., 2009). Thus, *A. blazei* (819 mg/kg) might produce significant antidepressant-like activity in unstressed mice by interaction with the serotonergic receptor and a_1-adrenoceptors, hence elevating the serotonin and norepinephrine levels. The level of monoamines like serotonin and norepinephrine decreased in depression, so drugs like monoamine oxidase (MAO) inhibitors and tricyclic antidepressants (TCAs) which increase the level of these monoamines are used to treat depression (Porsolt et al., 1977). 7-nitroindazole, neuronal nitric oxide synthase (nNOS), the inhibitor has been investigated to have antidepressant-like activity in unstressed mice (Tsuchiya et al., 1977). When 7-nitroindazole was administered to unstressed mice, which were already treated with the extract (819 mg/kg), there was no significant reduction in the immobility time when compared with *A. blazei* and 7-nitroindazole *per se*, suggesting that the antidepressant activity of *A. blazei* is not through nNOS inhibition.

Significantly reduced plasma nitrite levels were observed in unstressed mice administered 7-nitroindazole individually when compared with the vehicle control group. Although it did not enhance the plasma nitrite, however the decreasing effect of the extract in unstressed mice when compared to *A. blazei* and 7-nitroindazole *per se* which strongly supports that the antidepressant-like activity of *A. blazei* is not due to the association of nNOS. Whereas, the antidepressant activity of *A. blazei* was not significantly reversed in stressed mice that were already treated with p-CPA, prazosin, or sulpiride which indicates that the antidepressant-like activity of *A. blazei* is not through the interaction of the monoaminergic system so, in stressed mice, there might be some other mechanisms involved in the antidepressant-like activity of *A. blazei*. Acute restraint stress in rodents significantly elevates expression of inducible NOS (Tsuchiya et al., 1977). Aminoguanidine, inducible nitric oxide synthase (iNOS) inhibitor administration to stressed mice pretreated with *A. blazei*, the immobility time was significantly decreased as compared to *A. blazei* and aminoguanidine *per se*, suggesting that the antidepressant-like activity of *A. blazei* might be through the inhibition of iNOS. The plasma nitrite levels were significantly decreased in stressed mice treated with ABM and aminoguanidine. This further supports that the antidepressant-like activity of *A. blazei* in stressed mice is due to iNOS.

The restraint stress decreases superoxide dismutase and catalase levels and increased lipid peroxidation (Kashif et al., 2003). It has been investigated through a series of studies that there exists a correlation between depre-

ssive disorders and oxidative stress, either in the blood or brain (Bilici et al., 2001; Michel et al., 2007). Further, it was known that the activities of antioxidant enzymes are decreased in patients diagnosed with major depressive disorder, while this effect is ameliorated with the use of antidepressants (Herken et al., 2007).

Many studies have demonstrated that plants having antioxidant activities have shown antidepressant-like effects in rodents (Singh et al., 2009; Prakash et al., 2018). *A. blazei* has proven itself as an excellent antioxidant herb (Hakime-Silva et al., 2013) this antioxidant potential of the herb might have played a role in the antidepressant-like activity of this magic mushroom. Furthermore, no significant change was observed in the locomotor function of stressed and unstressed mice with respect to their vehicle control groups, so it showed that *A. blazei* has no effect on locomotor activity. This observation highly supports our hypothesis that the antidepressant-like activity of *A. blazei* is specific and not a false positive.

Conclusion

The antidepressant-like activity of *A. blazei* in unstressed mice is probably through interaction with adrenergic and serotonergic systems, while the antidepressant-like activity of *A. blazei* in stressed mice is probably through inducible NOS inhibition and its anti-oxidant activity.

Ethical Issue

The animals were handled according to the requirements mentioned in "Guidelines for the care and use of laboratory animals 8th edition" (Garber et al., 2011).

Conflict of Interest

The authors have no conflict of interest.

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