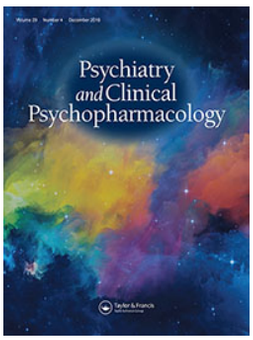

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Antidepressant-like activities of extracts of the fungus *Paecilomyces tenuipes* M98

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ABSTRACT

Objective: Depression is an disease that seriously endangers the physical and mental health of human body. However, in view of the limitation of existing antidepressants, it's urgent to find new antidepressants from natural products. The aim of this study was to evaluate the effect of *Paecilomyces tenuipes*, which is an important entomogenous fungus in China.

Methods: This research was intent to investigate the antidepressant actions of *P. tenuipes* M98 extracts using a battery of behavioural models including tail suspension test (TST) and forced swimming test (FST), 5-HTP-induced head twitch response and chronic unpredictable mild stress (CUMS) in mice.

Results: Fifteen days treatment with aqueous and ethanol extracts signifificantly decreased the duration of immobility in TST and FST, without signifificant changes in locomotor activity. Moreover, chronic application of extracts for 21 days signifificantly improved the depressive-like behaviours of CUMS mice, including reduced body weight and sucrose preference and lengthened immobility time in TST and FST. In addition, extracts produced a signifificant increase in 5-hydroxytryptamine and dopamine, but not noradrenaline, levels in hypothalamus. These fifindings suggested that this action of *P. tenuipes* might be related to the regulation of serotonergic and dopaminergic systems, which were further confirmed via 5-HTP induced head-twitch test. In addition, *P. tenuipes* M98 extracts also displayed anti-oxidative effffects.

Conclusion: *P. tenuipes* M98 extracts present excellent antidepressant-like activities, which might be explained by regulation of neurotransmitters and alleviation of oxidative stress.

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Paecilomyces tenuipes; antidepressant; antioxidative enzyme; monoamine neurotransmitters; chronic unpredictable mild stress

Introduction

Depression, also known as major depressive disorder, has become one of the most common affective disorders that endangers people's physical and mental health. The clinical symptoms of depression are persistent sadness, mental retardation, decreased physical activity, low self-esteem, diminished interest and cognitive function, suicidal tendencies and others [1]. In recent years, with the acceleration of the pace of life, fierce social competition, people's physiological and psychological pressure is growing. The incidence of depression is rising year by year and 300 million people have been reported to be suffering. According to a WHO report, there are about 322 million depressive patients worldwide, with a prevalence rate of about 44%. The prevalence rate of depression in China is 4.2%. It is estimated that depression will become the second leading cause of disability by 2020 [2,3]. Due to its high morbidity and mortality, depression produces great mental and financial burden to society and public health. Therefore, research on depression has become one of the focuses and hot topics of scientists.

Although there are many ways to treat depression, antidepressant medication is still widely used in clinical practice [4]. In the last 50 years, several kinds of antidepressants have been widely used for depression treatment. Although these antidepressants can improve some symptoms of depression, their clinical side effects are obvious, such as cardiotoxicity, hepatotoxicity, sexual dysfunction, diabetes, and hyponatremia [5]. Therefore, it is urgent to search for alternative antidepressants with less toxic side effects.

Entomogenous fungi are considered to be an ecologically highly specialized group of microorganisms, due to their plentiful pharmaceutically active compounds [6]. *Paecilomyces tenuipes*, one of the most popular

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entomogenous fungi in China, has various bioactive substances and bioactivities, including hypoglycemic, immunomodulatory and anti-tumor [7]. In the previous study, we had successfully obtained a mutant of *P. tenuipes*, named *P. tenuipes* M98, and proved that the mutant had high content of active substances and excellent anti-diabetic activity and safety. However, it is not clear whether the mutant can be used as a candidate for antidepressant therapy. Therefore, a series of animal models were used in the present study to investigate its antidepressant activity.

Materials and methods

Experimental animals

Male mice (18–22 g) were purchased from the Lab Animal Centre of Jilin University (Changchun, China; SCXK-(JI) 2007-0002). The animals were reared at 12:12 h light/dark cycle, temperature 23 ± 1°C, humidity 60 ± 2% and water and food available *ad libitum*. Animals were acclimatized and then used for experiments. All the experiments were conducted according to the guidelines of Jilin University.

P. tenuipes *M98 mycelium preparation*

P. tenuipes M98 used in the present study is a high yield strain obtained from *P. tenuipes* RCEF 4339 (Anhui Agricultural University, Anhui, China) by chemical mutation. This fungus was cultured at 26°C in a fermentation tank (100 L, Baoxing; China). The culture medium contained 40 g/L glucose, 10 g/L yeast extract powder and 10 g/L peptone following the protocol. The culture was incubated for 5 days at 26°C in a shaking incubator at 150 r/min. The mycelium were obtained by centrifugation (4000 × g, 8 min) and lyophilized.

Preparation of samples

Following the protocol of our previous study, we prepared water extract (WE) and alcohol extract from *P. tenuipes* M98 (AE) [8].

The experimental design of the behavioural despair test

A group of 10 mice was assigned to each of the eight treatments: Group CTRL (mice treated with physiological saline alone), Group Flu (mice administrated 2.50mg/kg fluoxetine hydrochloride orally for 15 days), Group AE (mice administrated orally 2.50, 0.25 and 0.05 g/kg alcohol extract daily for 15 days), Group WE (mice administrated orally 2.00, 0.20 and 0.04 g/kg of water extract for 15 days) as done previously [8].

After AE and WE treatment for 15 days, the forced swimming test (FST) was conducted [9]. In this test, each mouse was forced to swim for 6 min in a cylindrical glass tank (20 cm height, 14 cm diameter) containing 25 ± 1°C water (15 cm height). The first 2 min were considered habituation while the total immobility time was recorded during last 4 min. The criterion for immobility was that the mouse stop struggling in the water, just floating and only had movement to prevent its head from entering the water.

In addition, the tail suspension test (TST) was also performed [10]. In brief, the mouse was suspended at the end of its tail from a bar for 6 min with an adhesive tape at a height of 5 cm above the bottom. The total immobility time was recorded during the last 4min. The criterion for immobility was that the mice were completely motionless and just hung down passively.

The open-field test (OFT) was also employed to further investigate whether samples affect the locomotor activity of mice [11]. One mouse was put in the centre of a wooden box (50 cm × 50 cm × 40 cm) with 25 equal-area squares at the bottom. Observers recorded the number of squares passed by the mouse with its all paws (crossing) and rising of the front paws (rearing) respectively during a period of 5min.

5-Hydroxytryptophan-(5-HTP) induced head twitches test

The method was performed in a previous study [12]. Mice were divided into nine groups (10 mice/group). AE and WE (AE: 2.50, 0.25, 0.05 g/kg; WE: 2.0, 0.20, 0.04 mg/kg) and 2.50 mg/kg fluoxetine hydrochloride were orally administrated in mice for 15 days. One hour after the last administration, all mice were injected with 0.20 g/kg 5-HTP. The number of head swing in 15 min was recorded.

Chronic unpredictable mild stress-(CUMS) induced depression-like mice model

Mice were randomly divided into nine groups ($n = 10$): Group CTRL (normal mice treated with physiological saline alone), Group DM (depression-like mice treated with physiological saline alone), Group Flu (depression-like mice administrated 2.5 mg/kg fluoxetine hydrochloride orally for 15 days), Group AE (depression-like mice administrated orally 2500, 250 and 50 mg/kg of alcohol extract daily), Group WE (depression-like mice administrated orally 2000, 200 and 40 mg/kg of water extract) following the protocol [13]. All mice received 21 days of administration (once a day).

The CUMS mice were induced according to the literature previously described with minor modifications

[14]. All mice except the control group, were subjected to a randomly selected stimulus for 21 days. The stimulus included the following: water deprivation (24 h), deprivation of food (24 h), hot environmental stimulation (42°C, 5 min), forced swimming for 5 min in 4°C water, foot heat shock (40 s), tail clamping (1 min) and limited space for 1.5 h. In order to ensure unpredictability, there was no stimulus used for two or more consecutive days.

Body weight was recorded during the whole experiment. In this experiment, the TST, FST and sucrose preference test (SPT) were used to analyse the antidepressant action of *P. tenuipes* M98. SPT was performed as described previously. At the end of experiment, 1% (w/w) sucrose solution was provided to all mice for 3 days followed by normal water for another 1 d. Following 24 h food and water deprivation, the mouse was free to take both sucrose solution (1%) and water for 1 h. Then, the consumption of water and sucrose solution was recorded and the sucrose preference (SP) was calculated [15].

After the behavioural testing, the mice were euthanized via administration with 200 mg/kg pentobarbital (Sinopharm Chemical Reagent Co., Ltd). The hypothalamus was dissected, weighted, and homogenized with ice-cold physiological saline. The supernatants were obtained by centrifuging at 2500 rpm for 10 min and then subjected to the measurement of the levels of 5-hydroxytryptamine (5-HT), dopamine (DA), noradrenalin (NE) in hypothalamus using by enzyme-linked immune sorbent assay (ELISA) method (RD, USA). The activities of SOD, GSH-Px and levels of MDA in hypothalamus were also detected via colorimetric method following manufacturer's instructions (Nanjing Biotechnology Co. Ltd., Jiangsu, China).

Statistical analysis

Data obtained were expressed in terms of mean ± S.D. One-way analysis of variance (ANOVA) followed by Dunn's test was used for statistical significance analysis. $p \leq .05$ indicated that the results were different and statistically significant.

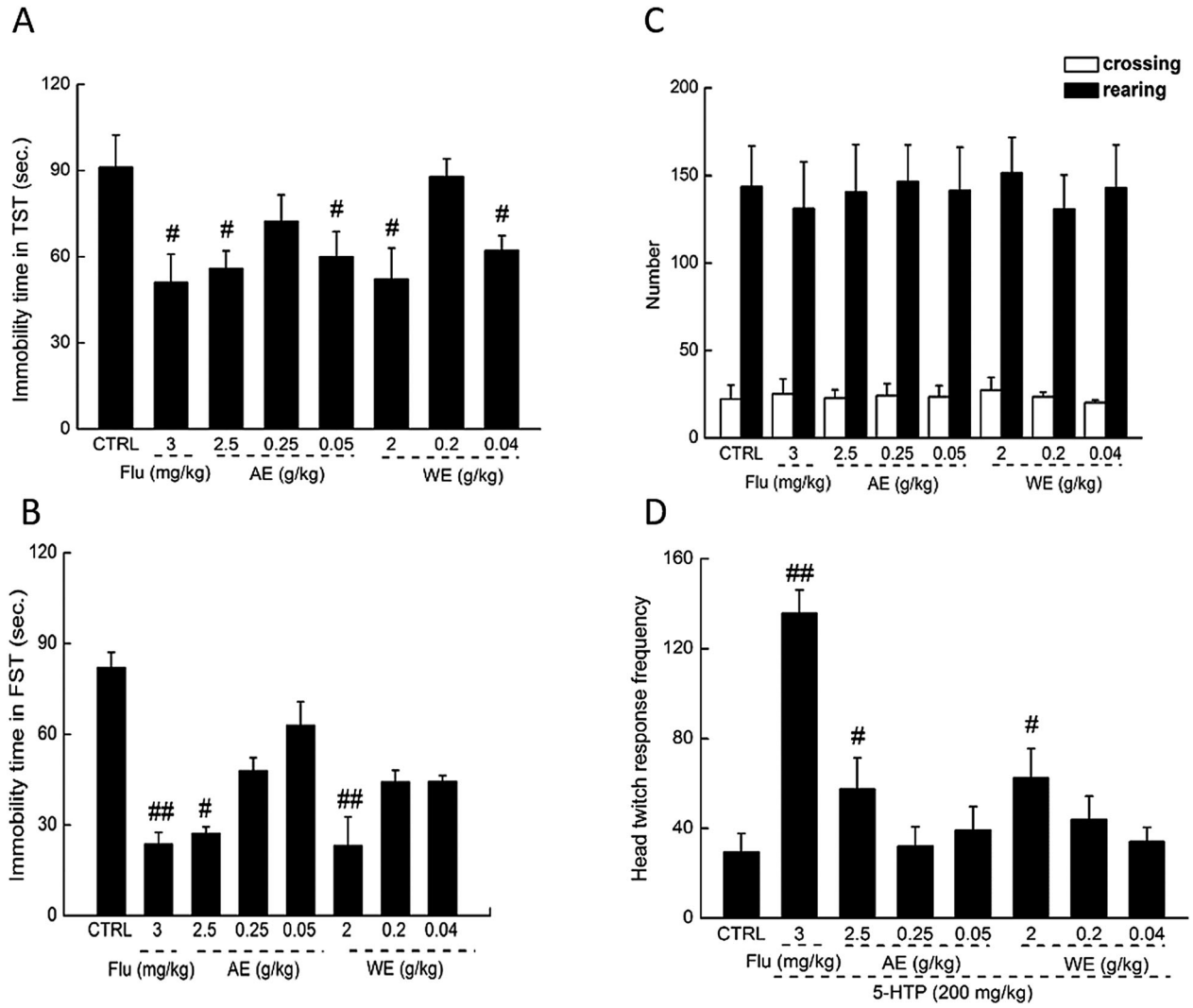

Figure 1. Effects of *P. tenuipes* M98 extracts on the immobility duration in TST (A) and FST (B) and the locomotor activity in mice (C). $^{\#}p < .05$ and $^{\#\#}p < .01$ versus non-treated mouse. (D) Effects of *P. tenuipes* M98 extracts on the number of head swings induced by 5-HTP. $^{\#}p < .05$ and $^{\#\#}p < .01$ versus non-treated mouse.

Results

Behaviour changes in the behavioural despair test

It can be seen that a decreasing tendency of immobility time was found in TST and FST after AE and WE administration. Statistical analysis demonstrated that fluoxetine, AE (2.50 and 0.05 g/kg) and WE (2.00 and 0.04 g/kg) administration significantly shortened the accumulative immobility time in TST ($p < .05$) (Figure 1(A)). Similarly, when mice were treated with fluoxetine, WE (2.00 g/kg) and AE (2.50 g/kg), the immobility time was significantly shortened during FST ($p < .05$; Figure 1(B)). In the ORF test, none of the samples modified the number of crossings and rearings compared with the mice treated with saline (Figure 1(C); $p > .05$).

Effect of P. tenuipes on 5-HTP induced head-twitch response in mice

Various degrees of promotion in head twitch number after 5-HTP treatment were observed after various treatments compared with non-treated group. Compared with the CTRL group, the number of head twitches was significantly increased (Figure 1(D); $p < .01$). High doses of AE and WE enhanced the head twitches number induced by 5-HTP after 15-day treatment (Figure 1(D); $p < .05$).

Antidepressant-like activities of P. tenuipes in CUMS-induced depression-like mice model

Effects of P. tenuipes on body weight and sucrose preference

Body weight of all the animals was measured on days 0, 10 and 21 of the experiment. Interestingly, after a variety of types of stimulation, the body weight of mice decreased. However, AE, WE and Flu administration for 21days restored the body weight of depression-like mice (Flu: $p < .05$, AE (2.50 g/kg): $p < .05$, WE (2.00 g/kg): $p < .05$ vs DM, respectively, Figure 2(A)).

At the beginning of the CUMS procedure, there was no obvious difference in SP between CTRL and exposure groups (Figure 2(B); $p > .05$). At the end of

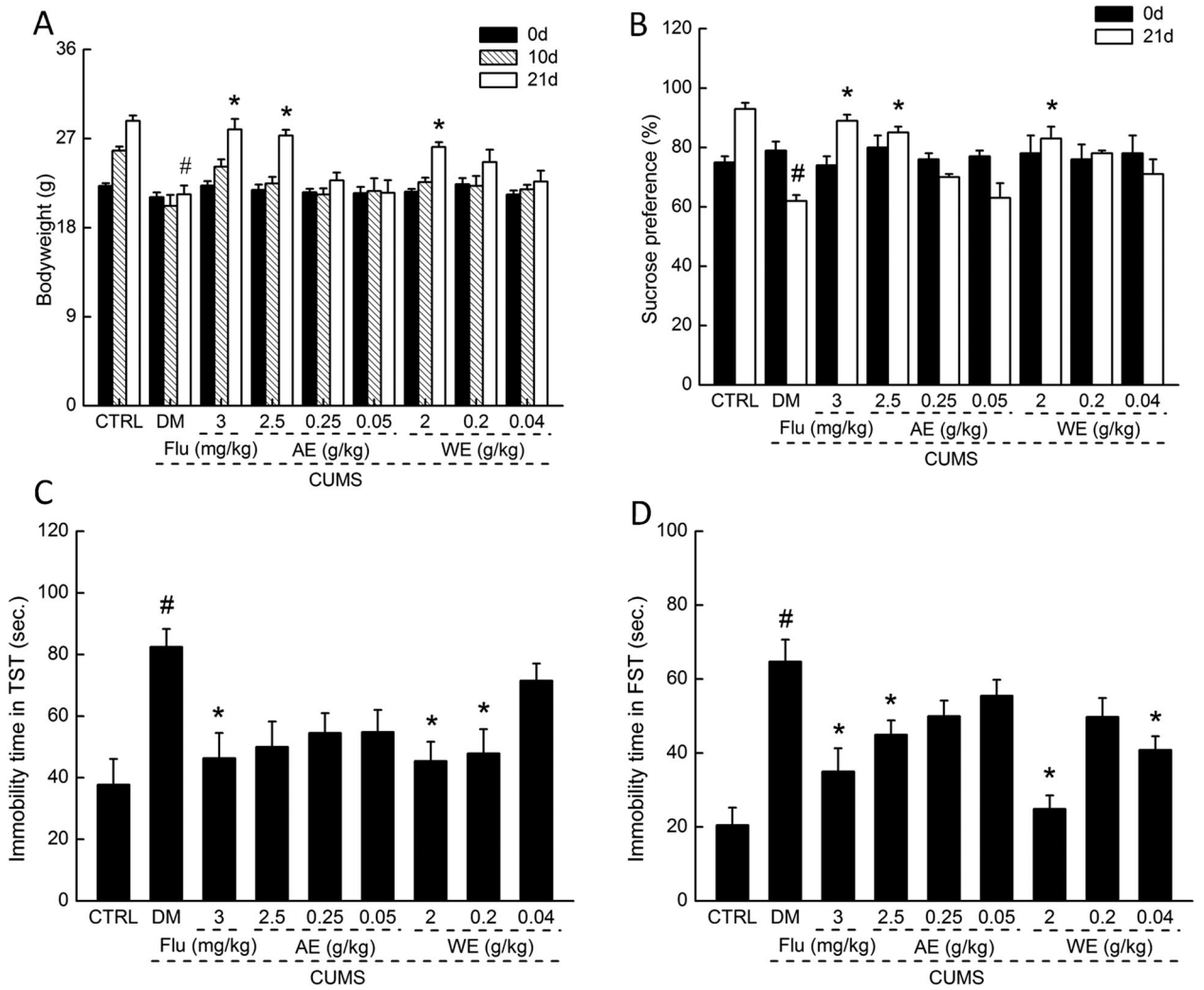

Figure 2. CUMS mouse model was established using a variety of mild stress. The changes of body weight (A), percent of sucrose consumption (B), the immobility duration in TST (C) and FST (D) were measured. $^{\#}p < .05$ versus controls. $^{*}p < .05$ versus model group.

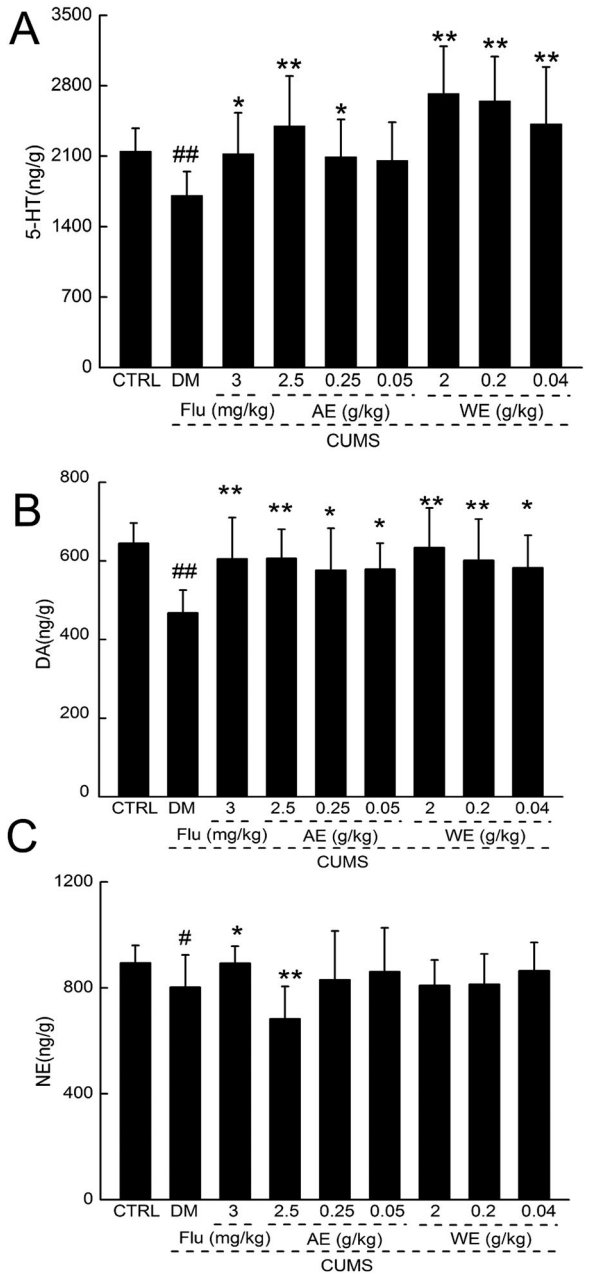

Figure 3. The effect of AE and WE administration on levels of 5-HT, DA and NE in the hypothalamus of all the mice. $^{\#}p < .05$ and $^{\#\#}p < .01$ versus control group; $^{*}p < .05$ and $^{**}p < .01$ versus model group.

the CUMS procedure, SP of mice exposed to different stimuli was significantly lower than that of normal animals ($p < .05$); while treatment with Flu and samples could alleviate the decrease of SP at different degree (Flu: $p < .05$, AE (2.50 g/kg): $p < .05$, WE (2.00 g/kg): $p < .05$ vs DM, respectively).

Effects of P. tenuipes *on behaviour in the FST and TST*

After stimulus for 21 days, the immobility time in TST and FST were significantly extended ($p < .05$). Statistical analysis showed that the immobility time was markedly shortened after Flu and *P. tenuipes* M98 extracts treatment in TST compared to DM group, (Flu: $p < .05$, WE (2.00, 0.20 g/kg): $p < .05$ vs DM, respectively, Figure 2(C)). Similarly, AE, WE and Flu administration obviously shortened the immobility time in FST (Flu: $p < .05$, AE (2.50 g/kg): $p < .05$, WE (2.00, 0.04 g/kg): $p < .05$ vs DM, respectively, Figure 2(D)).

Effects of P. tenuipes *on 5-HT, NE and DA levels in the mouse hypothalamus*

According to the monoamine hypothesis, the underlying pathophysiologic bases of depression are the insufficient functional availability of 5-HT, NE and/or dopamine DA [16]. These monoamine neurotransmitters are associated with regulation of mood, self-control, motivation, drive, and cognitive performance [17]. Thus, 5-HT, NE and DA concentrations in hypothalamus of mice were measured. As shown in Figure 3, after 21 days of stimulation, the levels of these three neurotransmitters in mice decreased significantly. Administration of Flu and samples enhanced the level of 5-HT in CUMS mice (Figure 3(A), Flu: $p < .05$, AE (0.25 g/kg): $p < .05$, AE (2.50 g/kg): $p < .01$, WE (three doses): $p < .01$ vs DM, respectively). Wang et al. reported similar results in terms of 5-HT, NE and DA concentrations in the hypothalamus and hippocampus of mouse [18]. In addition, Flu and extracts administration were able to enhance the concentration of DA in brain significantly (Figure 3(B), Flu: $p < .01$, AE (2.50 g/kg): $p < .01$, WE (2.00 and 0.20 g/kg): $p < .01$, AE (0.25 and 0.05 g/kg): $p < .05$, WE (0.04 g/kg): $p < .05$ vs DM, respectively). On the contrary, the NE concentrations of CUMS mice were not enhanced significantly after samples administration (Figure 3(C)).

Effects of P. tenuipes *on the activity of SOD and GSH-Px and MDA content*

As presented in Figure 4, the level of SOD and GSH-Px was obviously lower in CUMS mice than in normal mice (SOD: $p < .01$; GSH-Px: $p < .05$). While the concentration of MDA was increased significantly after stimulus for 21 days ($p < .01$). There were statistically significant differences in brain SOD activity of mice detected with all doses of samples and depression-like mice ($p < .05$). Meanwhile, administration of AE and WE at all doses remarkably decreased the activity of brain MDA ($p < .01$). In addition, GSH-Px activities were found to be increased in 0.25 g/kg AE and 2.00 g/kg WE groups (0.25 g/kg AE: $p < .05$; 2.00 g/kg WE: $p < .01$).

Discussion

Depression has become a serious mental health issue recently [19]. Unless appropriately treated, depression can cause serious consequences for patients, such as disability and suicide. In China, about 40% of suicides are caused by depression posing serious harm to patients' families [20]. Therefore, it is urgent to find

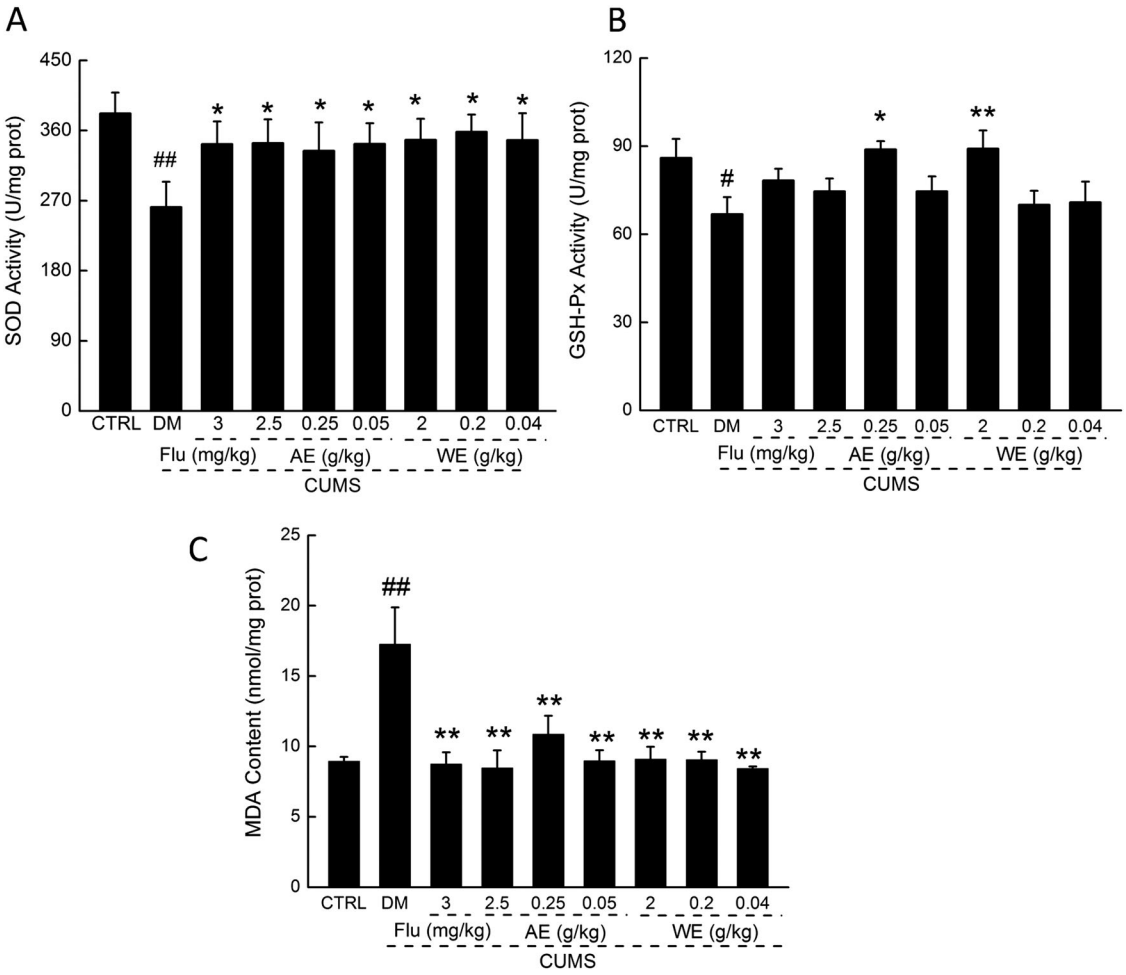

Figure 4. Anti-oxidative effects of *P. tenuipes* M98 extracts on normal and stressed mice. The levels of SOD (A), GSH-Px (B) and MDA (C) in brain were measured. $^{\#}p < .05$ and $^{\#\#}p < .01$ versus control mouse; $^{*}p < .05$ and $^{**}p < .01$ versus model group.

high efficacy and safety medicines to relieve this phenomenon. Previous reports indicated that many natural products which were extracted from fungi can be used in treating and preventing human diseases [21]. *P. tenuipes* is one of the most popular fungi in Asian nations, and is reported as valuable source of medicinal bioactive substances [22]. Our previous studies have shown that *P. tenuipes* M98 had high active ingredient content and safety. Based on the previous study, we, therefore, wondered whether this fungus has antidepressant activity. For screening antidepressants, various preclinical models were used. This research was intended to assess the antidepressant effects of *P. tenuipes* M98 using a battery of behavioural models like FST, TST, OFT, 5-HTP-induced head twitch response and CUMS in mice.

Firstly, the potential antidepressant-like effect of *P. tenuipes* M98 extracts was evaluated using FST and TST. These two depression behavioural models are commonly used for screening antidepressant-like activity of drugs [23]. Our data showed that both water and alcohol extracts of *P. tenuipes* M98 decreased the duration of immobility in these two depression behavioural models, reflecting the antidepressant-like action of *P. tenuipes* M98. However, other drugs tend to affect the results in FST and TST, such as convulsants, psychomotor simulants and anticholinergics. OFT was employed for assessing locomotor activity for the accuracy of the results with the FST and TST [24]. Our data confirmed that AE and WE had no locomotor activity.

It is well known that the concentrations of monoamines are closely related to the pathogenesis of depression [25]. The 5-HTP induced head twitches test was also employed to assess whether the antidepressant activity of the *P. tenuipes* M98 is related to activation of serotonergic neurones. In our study, the number of head twitches induced by 5-HTP was significantly increased by pretreatment with both AE and WE. The above action may be explained as an increase in the synaptic levels of serotonin [26].

In addition, CUMS was also used to assess the antidepressant effect of *P. tenuipes* M98. CUMS is thought to be one of the most valuable models for preclinical screening of new antidepressants [27]. It can mimic people facing unpredictable pressure every day and replicate several depression-related behavioural and physiological impairments [28]. In our present study, multiple chronic stress caused a significant decrease in the body weight, consistent with the findings of

others [29]. However, 21days of AE, WE and Flu administration significantly reduced weight loss. Reduced sucrose consumption in stressed animals is another essential indicator of anhedonia. Anhedonia is an important symptom of depression [30]. In this investigation, repeated administration of AE and WE ameliorated CUMS-induced decrease in sucrose consumption.

Following three consecutive weeks of chronic stress, the immobility time of mice in the TST and FST was increased significantly. Interestingly, treatment with AE and WE was capable of reversing CUMS-induced depressive-like behaviour by decreasing the immobility period, indicating significant antidepressant-like activity.

As we know, depression is closely associated with decreased function of monoamine in brain. Currently, most of antidepressant drugs are considered to elevate the functional availability of monoamines [31]. Thus, the level of 5-HT, DA and NE of CUMS-induced mice were analysed. Our data showed that after stimulus for 21 days, the level of these three neurotransmitters in stressed mice was obviously lower than that in normal mice, and the decrease of 5-HT and DA levels were reversed by administration of AE and WE. However, the NE concentrations of stressed mice were not enhanced significantly after AE and WE supplementation. Therefore, we inferred that the antidepressant effect of *P. tenuipes* M98 extracts might partially be mediated by its modulation of the monoamine neurotransmitters 5-HT and DA.

Lately, mounting evidence has indicated that oxidative stress also affects the development of depression [32]. The activities of SOD and GSH-Px, major antioxidant enzymes were measured in this study. Meanwhile, the level of MDA, which is the product of lipid peroxidation was also assessed. Consistent with previous findings, *P. tenuipes* M98 extracts also induced a marked decrease of SOD and GSH-Px activities and increased the MDA level of MDA by CUMS procedure. Administration of *P. tenuipes* M98 extracts reversed these changes, indicating that the antioxidant activity of *P. tenuipes* M98 has a potential relationship with its antidepressant effects.

Conclusion

In conclusion, these data using different behavioural and CUMS model indicated that *P. tenuipes* M98 extracts could possess an antidepressant effect. The antidepressant-like activity of *P. tenuipes* M98 might be explained by modulation of monoamine neurotransmitters (5-HT and DA) and alleviation of oxidative stress. Our primary investigation on the antidepressant-like effect of *P. tenuipes* M98 extracts will encourage the isolation of active principles responsible for antidepressant effect.

Disclosure statement

No potential conflict of interest was reported by the authors.

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