Antidepressant-like effect of essential oil of *Perilla frutescens* in a chronic, unpredictable, mild stress-induced depression model mice

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[ABSTRACT] *Perilla frutescens* (Perilla leaf), a garnishing vegetable in East Asian countries, as well as a plant-based medicine, has been used for centuries to treat various conditions, including depression. Several studies have demonstrated that the essential oil of *P. frutescens* (EOPF) attenuated the depressive-like behavior in mice. The present study was designed to test the anti-depressant effects of EOPF and the possible mechanisms in an chronic, unpredictable, mild stress (CUMS)-induced mouse model. With the exposure to stressor once daily for five consecutive weeks, EOPF (3, 6, and 9 mg·kg⁻¹) and a positive control drug fluoxetine (20 mg·kg⁻¹) were administered through gastric intubation to mice once daily for three consecutive weeks from the 3rd week. Open-field test, sucrose consumption test, tail suspension test, and forced swimming test were used to evaluate the behavioral activity. The contents of 5-hydroxytryptamine (5-HT) and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in mouse hippocampus were determined by HPLC–ECD. Serum interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α levels were evaluated by enzyme-linked immunosorbent assay (ELISA). The results showed that CUMS significantly decreased the levels of 5-HT and 5-HIAA in the hippocampus, with an increase in plasma IL-6, IL-1β, and TNF-α levels. CUMS also reduced open-field activity, sucrose consumption, as well as increased immobility duration in FST and TST. EOPF administration could effectively reverse the alterations in the concentrations of 5-HT and 5-HIAA; reduce the IL-6, IL-1β, and TNF-α levels. Moreover, EOPF could effectively reverse alterations in immobility duration, sucrose consumption, and open-field activity. However, the effect was not dose-dependent. In conclusion, EOPF administration exhibited significant antidepressant-like effects in mice with CUMS-induced depression. The antidepressant activity of EOPF might be related to the relation between alteration of serotonergic responses and anti-inflammatory effects.

[KEY WORDS] *Perilla frutescens*; ; Essential oil; Antidepressant; Anti-inflammation; Chronic unpredictable mild stress

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Introduction

Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure, decreased energy, feelings of guilt or low self-worth, disturbed sleep or appetite, and poor concentration. Today, depression is estimated to affect 350 million people (WHO, 2012). However, the exact mechanism underlying the development of depression and antidepressant action is still elusive. Studies on depression have focused on the interactions between the monoamine neurotransmitters and their reuptake and the receptor proteins. The current antidepressants available by chemical synthesis have a high incidence of dangerous side effects and are inadequate for number of individuals [1]. Accordingly, it is of great significance to research for and de-
velop more effective antidepressants with fewer drawbacks. Other mechanisms of depression development should also be considered, as they might provide potential effective targets with higher efficacy for the treatment of depression, and perhaps with lower adverse-effect.

Nowadays, more plant-based medicines are being used as alternative therapy for depression [2]. Plant-derived natural products in drug discovery and development have become the focus of attention for many scholars, in that plant extracts may have higher safety than synthetic drugs [3]. Perilla leaf is prescribed as one of the component herbs of such traditional Chinese herbal remedies as Banxia-Houpo-Tang and Xiang-Su-San, which are used clinically for the improvement of depressive mood, and for which antidepressant-like activities have been reported experimentally [4-5]. Pharmacological studies carried out with extracts from Perilla leaf show that this plant medicine exerts several biological effects, such as antitumor [6], anti-inflammatory [7], antioxidant [8], and anti-allergic [9] activities. This plant also shows antidepressant-like activity. A previous study demonstrated that the essential oil of *Perilla frutescens* (L.) Britton (Lamiaceae) (EOPF) produces an antidepressant-like effect, at least in part through restoring hippocampal BDNF expression in CUMS-induced mice [10], suggesting that EOPF might be useful for the prevention of depression. In this work, the antidepressant-like effect of the chronic administration of EOPF was investigated and its other possible mechanisms explored using a chronic stress depression animal model and biochemical test.

Stress is one of the most important factors responsible for depressive disorders [11]. The chronic unpredictable mild stress (CUMS) model, a widely used rodent model of depression, consists of repeated exposure to an array of varying and unpredictable, mild stressors over a sustained period of time (ranging from 10 days to 8 weeks) [12]. Since the inception of this model 20 years ago, the CUMS model of depression has been widely used in preclinical antidepressant screening to investigate the pathophysiology of depression and the associated therapeutic interventions [13-14]. With exposure to CUMS, animals appear to exhibit behavioral disturbances and neurobiological changes which are similar to the symptoms and presumed neurobiological changes of depression in humans, including anhedonia, behavioral despair, and lack of acute activation. Moreover, chronic mild stress could induce a pro-inflammatory response in the brain and other systems mainly characterized by a complex release of several inflammatory mediators, such as cytokines, prostanoids, free radicals, and transcription factors, which may be related to one of the possible mechanisms in the pathophysiology of depression disorder [11]. In patients with major depression, or in animal models of depression, significant increases in the concentrations of pro-inflammatory cytokines have been consistently reported [15]. There has been increasing interest in the role of cytokine-mediated inflammation in physiologically adverse conditions [16-17]. Increasing evidence indicates that inflammatory processes and brain-immune interactions are involved in the pathogenesis of depression, and increased levels of pro-inflammatory cytokines, e.g. interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α, have consistently been reported in patients with depression [18-20]. Studies have demonstrated that cytokines can influence the metabolism of the neurotransmitters, serotonin, norepinephrine, and dopamine, and alter neuroendocrine function [17-21-23]. It is also well-known that monoamine neurotransmitters or their metabolites, such as 5-hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) in the central nervous system play a key role in the pathophysiology of depression. These cytokine-induced changes in neurotransmitter and neuroendocrine function have, in turn, been correlated with the development of depression [24].

The aim of the present study was to explore possible antidepressant-like effects of EOPF and its possible mechanism. 5-HT and 5-HIAA levels were analyzed in the hippocampus and IL-1, IL-6, and TNF-α in the plasma of the experimental animals to investigate whether EOPF had inflammatory effects, and whether this activity was related to the antidepressant-like effect.

**Methods and Materials**

**Reagents and assay kits**

Fluoxetine hydrochloride was purchased from Changzhou Siyao Pharmaceuticals Co., Ltd. (Changzhou, China). ELISA kits (R&D, Minneapolis, MN, USA). *Perilla frutescens* (Perilla leaf) was purchased from Xiansheng drug Store (Nanjing, China) and was authenticated by Prof. Min-Jian Qin (Department of Medicinal Plants, China Pharmaceutical University, Nanjing, China). 5-HT and its metabolite 5-HIAA were purchased from Sigma (St. Louis, MO, USA) and were dissolved in the extract solution.

**Experimental animal**

Male ICR mice weighing 18–22 g were purchased from the Experimental Animal Center in Jiangsu Province (Nanjing, China). Mice were randomly housed in cages for one week to adapt to their environment before being used experimentally. Standard laboratory conditions were temperature (25 ± 1) °C and a 12-h light/12-h dark cycle with food and water available *ad libitum* for the duration of the study. All the experiments and animal care were performed strictly in accordance with the Provision and General Recommendations of the Chinese Experimental Animals Administration Legislation, and were approved by the Science and Technology Department of Jiangsu Province.

**preparation of EOPF**

The essential oil of *P. frutescens* was extracted by the method of steam distillation as described before [25]. Four hundred grams of the chopped perilla leaf with eight times the amount of distilled water was put into the volatile oil extractor,
and the time of extraction was six h. The essential oil was mixed with 0.03% sodium carboxymethyl cellulose (CMC-Na) at concentrations of 0.5, 1.0, and 1.5 μL·mL⁻¹. The control treatment was 0.03% CMC-Na.

**CUMS procedure**

The CUMS procedure was established according to a previous study [29], except for minor modifications. In brief, mice in the CUMS groups were exposed to a variety of mild stressors: (1) food deprivation for 24 h, (2) water deprivation for 24 h, (3) cage tilt (45°) for 7 h, (4) exposure to an empty bottle for 1 h, (5) overnight illumination, (6) forced swimming at 8 °C for 6 min, (7) soiled cage (200 mL water in 100 g sawdust bedding) for 24 h, (8) physical restraint for 2 h, and (9) exposure to a foreign object (e.g., a piece of plastic) for 24 h. Mice received one of these stressors per day in the sequence shown above, and the same stressor was not applied continuously for two days. The stress procedure lasted for six weeks prior to behavioral testing.

**Drug treatments and experimental design**

The animals were divided into five treatment groups (10 mice per group) as follows: vehicle-control (0.03% CMC-Na), vehicle-CUMS (0.03% CMC-Na), CUMS-fluoxetine (20 mg·kg⁻¹), CUMS-EOPF treatments (3, 6, and 9 mg·kg⁻¹). All drugs were administered by the oral route (p.o.) once a day during the last three weeks of the CUMS procedure and the administration volume was 10 mL·kg⁻¹.

**Open-field test (OFT)**

In order to assess possible effects of drug treatment on spontaneous locomotor activity, the animals were submitted to the open-field paradigm, as previously described [27]. Briefly, mice were individually placed in a wooden box (40 cm × 60 cm × 50 cm) with the floor of the arena divided into 12 equal squares. Each mouse was placed individually into the center of the arena and permitted free exploration. The numbers of squares crossed by the mice (crossings) and of standing on the hind legs (rearings) were recorded during a three min test. This apparatus was cleansed with a detergent and dried after occupancy by each mouse.

**Forced swimming test (FST)**

The forced swim test (FST) was similar to the traditional method that is described in a detailed reference [24], with some modifications. Briefly, mice were individually forced to swim in an open cylindrical container (diameter 14 cm, height 20 cm), containing 10 cm of water (depth) at (25 ± 1) °C. Each animal was forced to swim for six min, and the total duration of immobility was measured during the last four min. The definition of immobility was the absence of all movements, with only motions required to maintain the animal’s head above the water. Observers were blind to the group treatment of the mice.

**Tail suspension test (TST)**

The tail suspension test was performed based on a previous publication [29]. Briefly, mice both acoustically and visually isolated were suspended 50 cm above the floor by adhesive tape placed approximately 1 cm from the tip of the tail. The total test duration of mouse immobility was quantified during a test period of 6 min. Mice were considered immobile only when they were passively suspended and remained completely motionless.

**Sucrose preference test**

The sucrose preference test was performed as previously described [30], with some modifications. Briefly, 72 h before the test, mice were trained to adapt to 1% sucrose solution (W/V): two bottles of 1% sucrose solution were placed in each cage, and 24 h later 1% sucrose in one bottle was replaced with tap water for 24 h. At the end of the adaptation, mice were deprived of water and food for 24 h, followed by the sucrose preference test, in which mice were housed in individual cages and had free access to two bottles with sucrose solution (100 mL, 1%, W/V) and tap water (100 mL), respectively. Twelve hours later, sucrose and water consumption (mL) were recorded, and the sucrose preference was calculated as the sucrose preference (%) = sucrose consumption / (sucrose consumption + water consumption).

**Blood and brain sampling collection**

Mice were sacrificed by cervical dislocation. Blood was collected through cardiac puncture and sampled into plain tubes. The blood sera were obtained following a 20-min centrifugation at 3 000 g (Hermle Z 300K) at 4 °C, and stored at –80 °C. The hippocampus was rapidly dissected from the brain of the sacrificed mice and placed on an ice-chilled glass plate and stored at –80 °C.

**Determination of 5-HT and 5-HIAA levels in the mouse brain**

5-Hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) were measured by HPLC coupled with an electrochemical detector (ECD, LC-4C, BAS, West Lafayette, IN, USA) (10 nA range, 1 Hz filter, and 0.510V AppE cell) and an autosampler (CMA 200 refrigerated microsampler, Stockholm, Sweden), as described previously [31]. The mobile phase was composed of 0.17 mol·L⁻¹ NaH₂PO₄, 0.63 mmol·L⁻¹ ethylenediaminetetraacetic acid (EDTA), 0.60 mmol·L⁻¹ octane-l-sulfuric acid sodium salt (SOS), 2.0 mmol·L⁻¹ KCl, and 20% methanol, and adjusted to pH 3.11 with 85% H₃PO₄. The mobile phase was filtered through a 0.2 μm filter, degassed, and delivered at a flow rate of 500 μL·min⁻¹. The isolated hippocampus was homogenized in extract solution (2 mL). The extract solution consisted of 0.1 mol·L⁻¹ HCl containing 10⁻⁷ mol·L⁻¹ ascorbic acid, 15 mg·L⁻¹ pargyline, and 50 pg·μL⁻¹ isoproterenol. Certain volumes of each sample were centrifuged at 10,000 g for 20 min at 4°C. After filtration through a 0.45 μm filter, the supernatant was injected into a reverse-phase ion pair HPLC-ECD. Chromatographic separations were performed on ODS (C₁₈, 5 μm particle size, 25 cm × 4.6 mm inner diameter), purchased from Luna (Phenomenex Inc., Torrance, CA, USA). The identification and purity of the chromatographic peaks, as well as their quantitative evaluation, was performed with respect to peaks obtained from external standards (5-HT and 5-HIAA).
IL-1, IL-6, and TNF-α levels determinations

Commercial ELISA kits were applied for the detection of IL-1, IL-6, and TNF-α in serum samples obtained from treated or untreated mice following the instructions supplied by the manufacturer and quantified by an ELISA reader (450 nm). The results are shown as pg of cytokine per 100 mg of tissue or pg·mL⁻¹.

Statistical analyses

Data in the figures or table are presented as the means ± SD. Comparisons between experimental and control groups were performed by one-way analysis of variance (ANOVA) followed by post hoc Fisher’s least significant difference (LSD) test. The probability levels of $P < 0.05$ or $P < 0.01$ were considered to be statistically significant.

Results

Effects of EOPF on locomotor activity in open-field test

The open-field test was performed 24 h after the last stressor in the chronic stress model. Chronic stress significantly induced a reduction of the crossings, rearings, and groomings, while EOPF (3 and 6 mg·kg⁻¹) or fluoxetine hydrochloride (20 mg·kg⁻¹) reversed these effects (Table 1).

<table>
<thead>
<tr>
<th>Group</th>
<th>Doses (mg·kg⁻¹)</th>
<th>Crossings (mean ± SD)</th>
<th>Rearings (mean ± SD)</th>
<th>Groomings (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>—</td>
<td>72.1 ± 15.2</td>
<td>15.8 ± 4.60</td>
<td>2.25 ± 0.92</td>
</tr>
<tr>
<td>Stress + vehicle</td>
<td>—</td>
<td>46.2 ± 17.6*</td>
<td>6.42 ± 4.35**</td>
<td>1.08 ± 0.86**</td>
</tr>
<tr>
<td>Stress + FLU</td>
<td>10</td>
<td>67.1 ± 25.7*</td>
<td>10.0 ± 2.74</td>
<td>1.92 ± 0.76*</td>
</tr>
<tr>
<td>Stress + EOPF 3</td>
<td>3</td>
<td>43.2 ± 21.5</td>
<td>10.3 ± 4.25*</td>
<td>2.00 ± 1.00*</td>
</tr>
<tr>
<td>Stress + EOPF 6</td>
<td>6</td>
<td>70.4 ± 18.9*</td>
<td>10.3 ± 3.66*</td>
<td>2.00 ± 1.15*</td>
</tr>
<tr>
<td>Stress + EOPF 9</td>
<td>9</td>
<td>62.3 ± 14.9*</td>
<td>7.00 ± 5.26</td>
<td>0.92 ± 0.86</td>
</tr>
</tbody>
</table>

Notes: *$P < 0.01$ vs the normal control group; **$P < 0.01$, *$P < 0.05$ vs the model group.

Effects of EOPF on immobility time in the forced swimming test

As shown in Fig. 1, CUMS-induced depressive mice exhibited a significant increase in immobility duration versus the control group ($P < 0.001$). Fluoxetine hydrochloride (20 mg·kg⁻¹) or EOPF at the doses of 3 and 6 mg·kg⁻¹ reduced the immobility duration in comparison with the CUMS group ($P < 0.01$, $P < 0.05$).

![Fig. 1](image1.png)

**Fig. 1** Effects of EOPF on immobility time in the forced swimming test in CUMS-exposed mice (means ± SD, $n = 12$). Immobility duration was measured for the last four min of the forced swimming test. *$P < 0.01$ vs the normal control group; **$P < 0.01$, *$P < 0.05$ vs the model group.

Effects of EOPF on immobility time of tail suspension test

The tail suspension test data (Fig. 2) revealed that EOPF treatment at doses of 3 mg·kg⁻¹ ($P < 0.01$) or 9 mg·kg⁻¹ ($P < 0.05$) significantly reduced immobility time compared with the model group. The positive control fluoxetine (20 mg·kg⁻¹) significantly reduced immobility time in the TST ($P < 0.01$) compared with the model group. CUMS exposure significantly increased the immobility duration versus the control group ($P < 0.001$).

![Fig. 2](image2.png)

**Fig. 2** Effects of EOPF on immobility time in the tail suspension test in CUMS-exposed mice (means ± SD, $n = 12$). Immobility duration was measured for the last four min of the tail suspension test. *$P < 0.01$ vs the normal control group; **$P < 0.01$, *$P < 0.05$ vs the model group.

Effects of EOPF treatment on the percentage of sucrose consumption in CUMS-exposed mice.

Sucrose consumption was measured for 24 hours on the second day after the chronic stress period (means ± SD, $n = 12$). CUMS exposure significantly increased the sucrose consumption versus the control group ($P < 0.01$).

![Fig. 3](image3.png)

**Fig. 3** Effects of EOPF treatment on the percentage of sucrose consumption in CUMS-exposed mice. Sucrose consumption was measured for 24 hours on the second day after the chronic stress period (means ± SD, $n = 12$). *$P < 0.01$ vs the normal control group; **$P < 0.01$, *$P < 0.05$ vs the model group.
Effects of EOPF on sucrose consumption

Fig. 3 shows the effects of EOPF treatment on the percentage of sucrose consumption in CUMS-exposed mice. CUMS exposure significantly reduced the percentage of sucrose consumption in the animals as compared to the control \((P < 0.001)\). Chronic treatment with EOPF at daily doses of 3 or 9 mg·kg\(^{-1}\) significantly increased the percentage of sucrose consumption in CUMS-exposed mice as compared to the vehicle-treated and CUMS-exposed mice \((P < 0.05)\). Treatment with fluoxetine \((20 \text{ mg·kg}^{-1})\) also significantly increased the percentage of sucrose consumption in CUMS-exposed mice \((P < 0.05)\).

Effects of EOPF on 5-HT and 5-HIAA levels in the hippocampus of mice after CUMS

As shown in Fig. 4, the 5-HT and 5-HIAA concentration was significantly lower in the hippocampus of CUMS-induced mice compared with the normal mice. The EOPF \((3 \text{ or } 9 \text{ mg·kg}^{-1})\) treatment significantly increased the concentration of 5-HIAA and 5-HT in the hippocampus \((P < 0.01)\) compared with model group; the 5-HT and 5-HIAA concentration was also significantly increased in the fluoxetine group compared with model group \((P < 0.01, P < 0.05\), respectively).

Fig. 4 Effects of EOPF treatment on 5-HT and 5-HIAA level in the hippocampus of CUMS-exposed mice (means ± SD, \(n = 12\)). \(*P < 0.01\) vs the normal control group; \(**P < 0.01, \*P < 0.05\) vs the model group

Effects of EOPF on serum IL-6, IL-1\(\beta\) and TNF-\(\alpha\) level in mice

Plasma IL-6, IL-1\(\beta\), and TNF-\(\alpha\) levels were measured at the end of the experiment (Fig. 5). Higher serum levels of pro-inflammatory cytokines than in controls were observed in the CUMS-exposed groups \((P < 0.001)\). EOPF treatment dose-dependently decreased the plasma IL-6, IL-1\(\beta\), and TNF-\(\alpha\) levels. Treatment with fluoxetine \((20 \text{ mg·kg}^{-1})\) also significantly decreased the plasma IL-6, IL-1\(\beta\), and TNF-\(\alpha\) levels \((P < 0.001)\).

Fig. 5 Effects of EOPF treatment on serum TNF-\(\alpha\) (A), IL-1\(\beta\) (B) and IL-6 (C) level in CUMS-exposed mice (means ± SD, \(n = 12\)). \(*P < 0.01\) vs the normal control group; \(**P < 0.01, \*P < 0.05\) vs the model group

Discussion and Conclusions

Chronic unpredictable mild stress (CUMS) is currently accepted as a better animal model of depression, and plays an important part in the evaluation and development of antidepressant drugs \([32]\). With exposure to CUMS, animals appeared to exhibit long-term behavioral disturbances resembling symptoms of clinical depression, and that the CUMS-induced depression model can be used for evaluating the efficacy of antidepressant candidates through behavioral tests like the sucrose preference test, open-field test, tail suspension test and forced swimming test. Sucrose consumption deficits have been regarded as the representation of ‘anhedonia’ induced by CUMS \([26, 33]\). The immobility of animals in the forced swimming test and the tail suspension test has been expected to reflect a state of ‘behavioral despair’ \([34]\). The locomotor activity in the open-field test has been taken as an indicator of emotional state \([35]\). Therefore, the open-field test, sucrose consumption test, tail suspension test, and forced swimming test are widely used to evaluate the behavioral activity in animal experiment. In the present study, the CUMS mouse model was successfully simulated for the depressive status by the reduction of sucrose intake, open-field activity, and the increase of immobility duration.

A deregulation of the bioactive neurotransmitter serotonin or 5-hydroxytryptamine (5-HT) has been suggested to play an important role in the pathogenesis of depression, and the mainstream of research in depression has principally fo-
cused on serotonergic systems [36]. Several studies have shown that chronic stress produces changes in the concentrations of neurotransmitters in mice, mainly exhibited as the significant decrease in the levels of 5-HT and its metabolite 5-HIAA in the brain [37-38]. The present data support these studies, whereby the CUMS mice exhibited decreased 5-HT and 5-HIAA levels versus the normal control group.

Chronic mild stress could induce a pro-inflammatory response. Pro-inflammatory cytokines, including IL-1, IL-6, and TNF-α, are released by activated immune cells during the host response to psychosocial stress. Pro-inflammatory cytokines in the blood access the central nervous system and interact with a cytokine network in the brain to influence virtually every aspect of brain function relevant to behavior including neurotransmitter metabolism, neuroendocrine function, synaptic plasticity, and neurocircuits that regulate mood, motor activity, motivation, anxiety and alarm [39]. The results from the present studies support this view showing that CUMS induced the elevation of serum pro-inflammatory cytokine levels.

In the present study, the CUMS mouse model was successfully simulated for the depressive status by the reduction of sucrose intake, open-field activity, and the increase of immobility duration, accompanied by a significant increase of serum IL-6, IL-1β, and TNF-α levels. Furthermore, the decrease of 5-HT level in hippocampus was also observed in the CUMS-induced mice. The CUMS mouse model with long-term EOPF treatment during the course of CUMS was found to alleviate CUMS-induced depression. In this study, it was found that chronic EOPF administration significantly reduced immobility time in the forced swimming test and increased the percentage of sucrose consumption in CUMS-exposed mice, which is in accordance with previous research results [10]. Further, it was also found that long-term EOPF administration affected the spontaneous locomotor activity, and 3 or 9 mg·kg⁻¹ EOPF effectively reduced immobility time in the TST-subjected mice. Chronic EOPF administration could significantly decrease the serum IL-6, IL-1β, and TNF-α levels accompanied by an increase of 5-HIAA and 5-HT levels in the hippocampus of CUMS-exposed mice. The results showed that there was an association between the metabolism of serotonin and the levels of IL-6, IL-1β, and TNF-α in CUMS-exposed mice. The results mentioned above suggest that inflammation does occur in the periphery, and is associated with depression-like behavior and a decrease in the levels of 5-HT and its metabolite 5-HIAA in the hippocampus. These results also showed that EOPF is an effective treatment for depression because it can reduce pro-inflammatory cytokines, as well as modulate 5-HT metabolism, and thus ameliorate the depression-like behavior. However, further studies should be conducted to investigate the molecular mechanism of the interaction between 5-HT metabolism and peripheral inflammation. In addition, since a previous study demonstrated that the antidepressant-like effect of EOPF is partly related to restoring hippocampal BDNF expression in CUMS-induced mice [10], the relationship between hippocampal BDNF expression and peripheral inflammation is an issue that needs to be explored in the future.

In conclusion, EOPF by oral administration appeared to exert significant antidepressant-like effects in the forced swimming test, tail suspension test, open-field test, and sucrose consumption test in the CUMS-induced depression model in mice. The mechanism of action may relate to the anti-inflammatory effects of EOPF.

References


