RESEARCH ARTICLE

The BDNF-TrkB-CREB signaling pathway involved in the antidepressant effect of Saikosaponin A in a CUMS mouse model

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Depression is a common mental disease, characterized by high prevalence, high recurrence rate, high disability rate, high death rate, and high suicide rate. At present, the pathogenesis of depression is still not clear, which brings great difficulties to clinical diagnosis and treatment. *Radix Bupleuri*, as a traditional Chinese medicine for the treatment of "Shaoyang syndrome" has been indicated to have an antidepressant effect in diversified animal models of depression. Saikosaponin A (SSa) is one of dominating active components for *Radix Bupleuri*. This study explored the effect of SSa in an animal model of depression induced by chronic unpredictable mild stress (CUMS) and investigated whether SSa played an antidepressant role by regulating the BDNF-TrkB-CREB signaling pathway. The established CUMS mouse model was treated with different concentrations of SSa at 15, 30, and 60 mg/kg. Behavioral tests were then conducted including sucrose preference test (SPT), open filed test (OFT), forced swimming test (FST), and the tail suspension test (TST). The mRNA levels of brain-derived neurotrophic factor (BDNF), tropomyosin receptor kinase B (TrkB), and cAMP-response element binding protein (CREB) in the hippocampus of CUMS mice were measured by reverse transcription-polymerase chain reaction (RT-PCR). The protein levels of BDNF, TrkB, pTrkB, CREB, and pCREB were measured by Western blot. The results showed that SSa significantly relieved CUMS-induced depressive-like behaviors in mice. SSa treatment significantly increased the sucrose preference and spontaneous activity in CUMS mice, while the immobility time in the forced swimming and the tail suspension test were shortened. In addition, SSa effectively inhibited CUMS induced mRNA reductions in BDNF, TrkB, CREB and up-regulated protein expression levels of BDNF, pTrkB, TrkB, pCREB, and CREB in the mouse hippocampus. The results indicated that SSa could effectively improve CUMS-induced depressive-like behavior in mice, which might be achieved by activating the BDNF-TrkB-CREB signaling pathway.

Keywords: depression; Saikosaponin A; chronic unpredictable mild stress; brain-derived neurotrophic factor; ropomyosin receptor kinase B; cAMP-response element binding protein.

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Introduction

Depression is a common mental disease that affects approximately 16% of the world's population [1]. Patients with depression demonstrate low spirits, loss of interest, guilt or inferiority, sleep anxiety or loss of appetite, insomnia or drowsiness, fatigue or energy loss, and poor concentration or difficulty in decision making [2]. The World Health Organization (WHO) predicts that depression may become the second leading cause of illness-induced disability

by the year 2030 [3]. Given that underlying pathogenesis with depression remains poorly understood, current treatments are not very effective. Antidepressants treat depression at less than half the rate of its occurrence and have obvious adverse reactions including loss of appetite, fatigue, and sexual dysfunction [4]. Therefore, it is urgent to identify novel effective and safe antidepressants.

In recent years, traditional Chinese medicine (TCM) has shown advantages of stable effects, fewer side effects, and lasting curative effects to treat depression [5]. Clinical experiments have shown that *Radix Bupleuri* has the effect of soothing the liver and relieving depression. Depression treatment with its compound prepared in the clinic has reported in aspects of inhibiting nerve inflammation, regulating monoamine transmitters of the nerves, inhibiting abnormal activity of the hypothalamic-pituitary-adrenal (HPA) axis, and enhancing expression of the brain-derived neurotrophic factor (BDNF) [6]. Saikosaponin A (SSa) is a soap-like component extracted from *Radix Bupleuri* that has various biological activities such as anti-inflammatory, analgesic, nerve-regulating, anti-fibrotic and anticancer [7]. Chronic unpredictable mild stress (CUMS) model was first proposed by Willner [8], in which animals were placed in unpredictable environments for approximately 3 - 4 weeks, and mild stimuli were given daily to observe the responses of animals to stimuli. The CUMS model is the most widely used depression model at present, which simulates the primary manifestation of long-term chronic low-intensity stimulation in human daily life and has the advantages of in accordance with the clinical characteristics of the disease, good repeatability, simple, reliable and maneuverability stable in state, long in duration and convenient for observation [9].

It has been reported that the BDNF-TrkB-CREB signaling pathway is involved in the survival, growth, and plasticity of nerve cells in the human brain and is closely related with depression [10]. BDNF is one of the important neurotrophic factors in the central nervous system that plays an important role in the development of the central nervous system and the survival, differentiation, growth, and development of neurons. Previous studies have shown that the content of BDNF decreases in both the central and peripheral regions of depression patients, and treatment with antidepressants restores the normal level, indicating that the pathogenesis of depression is related to BDNF [11]. Mature BDNF activates high-affinity receptor TrkB to promote receptor TrkB self-phosphorylation (pTrkB) [12]. The research showed that, in a model of chronic stress depression, expression of pTrkB/TrkB protein in the brain was downregulated, which induced depression-like behavior [13]. CREB is an important transcription factor induced by adenylate cyclase (AC) that transforms adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP) [14]. Expression CREB and pCREB mRNA and protein was significantly downregulated in a CUMS-induced depression rat model, and antidepressant treatment reversed this downregulation [15]. Previous study found that SSa had an antidepressant effect on male SD rats induced by CUMS. The mechanism of this effect might be related to its promotion of the expression of BDNF protein and mRNA in the hippocampus [16]. Experimental data indicated that SSa at 50 and 100 mg/kg improved behavior in perimenopause-like depression induced by CUMS in female Wistar rats, which might be mediated by upregulation of protein expression in the BDNF-TrkB signaling pathway [17].

The specific antidepressant mechanism of SSa has not been reported. The BDNF-TrkB-CREB pathway has been proven to be closely related to depression by regulating neurotrophic factors, inflammation, and neuroplasticity, all of which are involved in the occurrence and development of depression. This study evaluated the antidepressant effect of SSa in depressed male Kunming mice induced by CUMS and revealed the possible mechanism of the antidepressant of SSa through a systematic examination of the BDNF-TrkB-CREB pathway. The results of this

study provided favorable evidence for the identification of novel antidepressants.

Materials and methods

Experimental animal and CUMS model construction

A total of 55 healthy, male, clean Kunming mice, aged 4 weeks with the body weight from 18 - 24 g were obtained from the Harbin Medical University Animal Center (Harbin, Heilongjiang, China). The animals were housed at a temperature of 22 ± 1°C, relative humidity of 55 ± 5%, 12 h-light/dark cycle environment with 5 animals per cage and free access to food and water. All experimental procedures were approved by the Animal Ethics Committee at Harbin Medical University (Harbin, Heilongjiang, China). After one week of acclimation, behavioral assessment was conducted based on open filed test (OFT). 8 mice were randomly selected as the control group, while the remaining mice were subjected to CUMS treatment. The mice in the model group randomly received 12 types of stimulation including restraint (2 h), a cage tilted 45 degrees overnight, cage rotation (1 h), overnight isolation overnight, food deprivation, overnight water deprivation, noise pollution at 80 dB for 2 h using Retekess Tr110 radio (Zhengzhou Jierui Communication Co., Ltd., Zhengzhou, Henan, China), no packing overnight, day and night reversed, overnight using LFFM-20 stroboscope (Shanghai Beilan Optoelectronic Technology Co., Ltd., Shanghai, China), wet bedding overnight, and crowding overnight [18]. Two random methods were applied each day for 56 days with no same stress pattern being used for 2 consecutive days. Non-stressed mice (control group) were left undisturbed in their cages, except for necessary procedures such as regular cage cleaning.

Experimental grouping and treatments

After 28 days' exposure to the CUMS procedure, 40 successfully constructed CUMS mice were evenly divided into 5 groups with 8 mice in each group and received different type and dose of drugs intragastrically at 0.4 mL/kg once daily at 9:00 a.m. for a further 28 days, which included CUMS group administrated 0.9% sodium chloride solution, CUMS + 3 mg/kg fluoxetine (FLU) (People's Hospital, Daqing, Heilongjiang, China), CUMS + 15-mg/kg SSa-L, CUMS + 30-mg/kg SSa-M, and CUMS + 60 mg/kg SSa-H group. SSa was obtained from Ruifensi Biotechnology Co., LTD (Chengdu, Sichuan, China).

Behavioral tests

(1) Body weight (BW)

BW was obtained on experimental days 0, 7, 14, 21, 28, 35, 42, 49, 56.

(2) Sucrose preference test (SPT)

SPT was conducted at the end of the fourth and eighth week, 1 h after the last drug treatment of CUMS exposure to measure success of the model and behavioral changes after administration [19]. Before the test, mice were adapted to the 1% (w/v) sucrose solution. Two bottles of sucrose solution were placed in each cage for 24 h, and then one bottle of sucrose solution was replaced with tap water for 24 h. After adaptation, mice were deprived of water and food for 12 h. The test was conducted at 8:30 a.m. The mice individually had free access to two bottles. After 12 h, the volumes of the consumed sucrose solution and water were recorded. Sucrose preference (SP) values were calculated as below.

$$SP = \left(\frac{\text{sucrose intake}}{\text{sucrose intake} + \text{water intake}}\right) \times 100\%$$

(3) Open field test (OFT)

Locomotor activity and exploratory behavior of each mouse was assessed using the OFT as illuminated by previous studies [20]. OFT was performed on day 57. The open-field apparatus consisted of a 50 cm × 50 cm × 40 cm square arena with black walls and black base, of which the base was divided into 5 × 5 equal squares with legible white lines. Each mouse was gently placed in the center of the open-field floor and then allowed to enjoy independent movement and explore freely for 5 min. The numbers of crossings, rearings, and groomings were

monitored and recorded. After each trial, 75% ethyl alcohol was used to refresh the open-field apparatus to get rid of interfering odor signals.

(4) Tail suspension test (TST)

TST was done on day 58 to assess antidepressant activity [21]. The total duration of immobility induced by tail suspension was measured. The length of immobility time reflected the degree of despair in mice. After the last OFT, mice were suspended 50 cm above the floor for 6 min by adhesive tape placed approximately 1 cm from the tip of the tail. Immobility time during the final 4 min of the testing period was recorded. Mice were considered immobile only when they hung passively and completely motionless.

(5) Forced swimming test (FST)

FST was conducted on day 59. An individual mouse was placed softly into a 20 cm diameter glass cylinder filled to 20 cm in depth with 24 ± 1℃ water for 6 min. Mouse immobility and struggling behavior during the last 4 min swim session were recorded and quantified [22]. Struggling was defined as vigorous movements of the forepaws breaking the water, and immobility was defined when mice floated without struggling, making only those movements necessary to keep their head above the water. The glass cylinder was replaced with fresh water after each experiment. The time of immobility reflected the degree of despair in mice.

Sample collection

24 hours after completion of the forced swim test, mice were euthanized by rapid decapitation. Whole brains were rapidly removed and chilled in an ice-cold saline solution. The hippocampus was dissected on a cold plate and immediately frozen in liquid nitrogen. Tissue samples were stored at -80℃ until use.

qRT-PCR

Total RNA was extracted using TRIzol (Invitrogen, Carlsbad, CA, USA). cDNA was then reverse transcribed by using PrimeScript™ RT Kit with gDNA Eraser (Takara, Harbin, Heilongjiang, China) [23]. qRT-PCR was performed using SYBR® Premix Ex Taq™ II (Takara, Harbin, Heilongjiang, China) with LightCycler 480 apparatus (Roche Molecular Systems, Inc., Pleasanton, CA, USA) and primers of GAPDH forward (5'-GGT TGT CTC CTG CGA CTT CA-3') and reverse (5'- TGG TCC AGG GTT TCT TAC TCC-3'), BDNF forward (5'-TCA TAC TTC GGT TGC ATG AAG G-3') and reverse (5'-AGA CCT CTC GAA CCT GCC C-3'), TrkB forward (5'-GGC TTG ACA TCA TTG GCT GAC-3') and reverse (5'-CAT TGG GCC GAA CTT TCT GGT-3'), CREB forward (5'-CCT GTT TGA TCG GCA GGA C-3') and reverse (5'-CGG GGG ACC ATA ATG GAG A-3'). GAPDH was used as an internal control. Relative gene expression was calculated by the 2-ΔΔCq method.

Western blot

The entire hippocampus was homogenized in RIPA lysis buffer containing protease inhibitors and phosphatase inhibitors for protein extraction [24]. Supernatants were collected by centrifugation at 12,000 rpm for 15 min at 4°C, and total protein concentrations were determined by BCA assay (Beyotime, Daqing, Heilongjiang, China). Protein samples were separated by 10% SDS-PAGE gel electrophoresis and transferred onto NC membranes. After blocking with 5% non-fat dried milk, membranes were incubated with the antibodies of BDNF (1:500 dilution), TrkB (1:2,000 dilution) (Proteintech, Rosemont, IL, USA), pTrkB (1:1,000 dilution) (Bioss, Woburn, MA, USA), CREB (1:2,000 dilution) (Proteintech, Rosemont, IL, USA), pCREB (1:500 dilution) (Signalway antibody, Greenbelt, MD, USA), and β-actin (1:5,000 dilution) (Cell Signaling Technology, Danvers, MA, USA) at 4°C overnight. Subsequently, membranes were rinsed three times with TBS-T followed by incubation with goat anti-rabbit HRP-conjugated IgG (1:20,000 dilution) and goat anti-mouse HRP-conjugated IgG (1:10,000 dilution) (Zhongshan Jinqiao Biotechnology Co., Ltd, Beijing, China) secondary antibodies for 1 h at room temperature. Blots were washed three times with TBS-T and successively visualized with an enhanced chemiluminescence (ECL) system. Protein bands were quantified using AI600 Imaging System

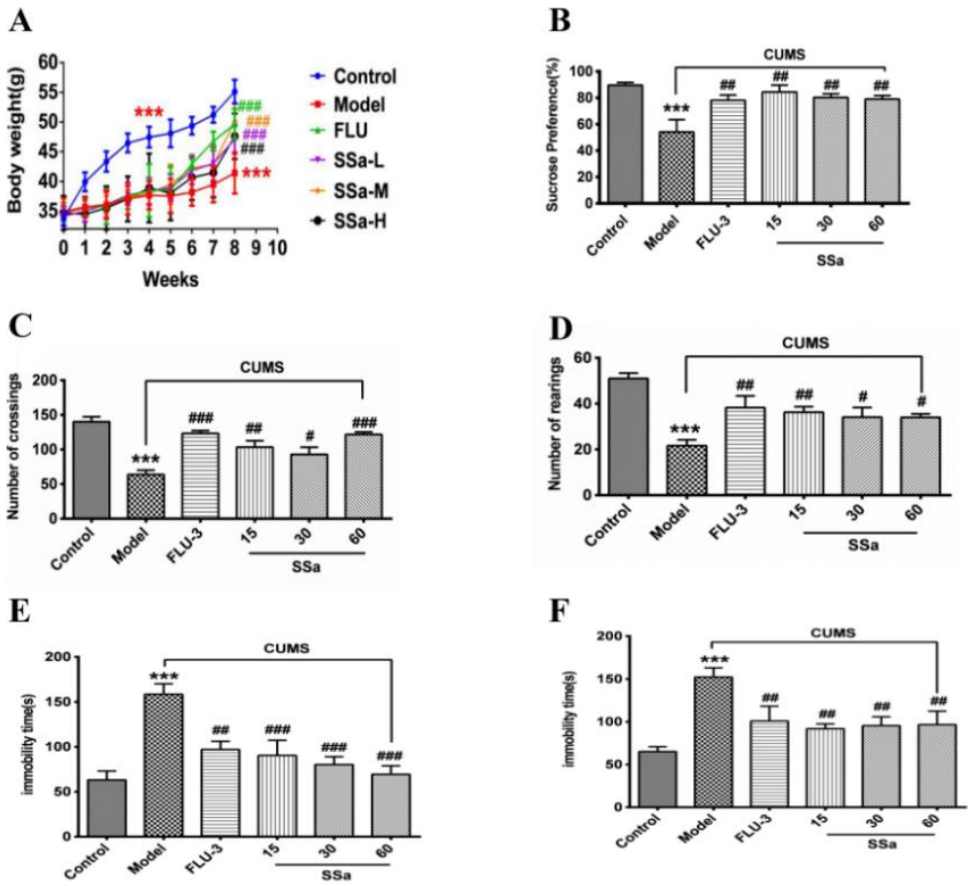


Figure 1. Body weight and behavioral tests. **A.** Body weights. **B.** Sucrose preference test. **C.** Open field test-crossings. **D.** Open field test-rearings. **E.** Tail suspension test. **F.** Forced swim test. ***: $P < 0.001$ *vs*. control group. $^{\#}$: $P < 0.05$, $^{\#\#}$: $P < 0.01$, $^{\#\#\#}$: $P < 0.001$ *vs*. model group.

(Cytiva, Marlborough, MA, USA).

Statistical analysis

All data were expressed as mean ± standard error of the mean (SEM). One-way ANOVA followed by Dunnett's multiple comparisons test was performed. *P* value less than 0.05 was considered statistically significant. Figures were created using GraphPad Prism (version 6) (https://www.graphpad.com/).

Results

Body weight

The results showed that, from 1 to 8 weeks, body weights were significantly decreased in the model group compared to the control group ($P < 0.001$). The body weights significantly increased in SSa treatment groups compared to that in the model group and fluoxetine group at week 8 ($P < 0.001$) (Figure 1A). These results suggested that SSa improved depressive-like symptoms by increasing appetite in CUMS mice.

Sucrose preference test

SPT results showed that CUMS mice demonstrated anhedonia behavior with decreased sucrose consumption compared to the control group ($F(5, 42) = 5.801$, $P < 0.001$). Four-week treatment with all different doses of SSa significantly increased sucrose consumption in CUMS mice ($P < 0.01$), and this effect was similar to that of fluoxetine group ($P < 0.01$) (Figure 1B). These results indicated that SSa might play an antidepressant role by improving anhedonia behavior in mice.

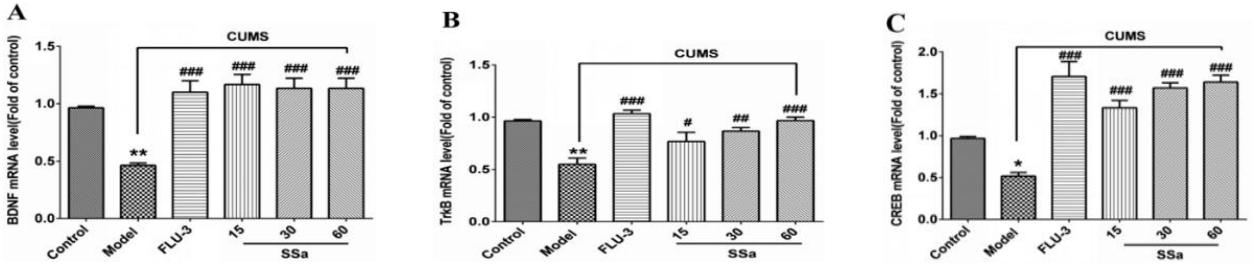


Figure 2. Hippocampal mRNA expression of BDNF (**A**), TrkB (**B**), and CREB (**C**). *: $P < 0.05$, **: $P < 0.01$ *vs*. control group. $^{\#}$: $P < 0.05$, $^{\#\#}$: $P < 0.01$, $^{\#\#\#}$: $P < 0.001$ *vs*. model group.

Open field test

Results of OFT showed that CUMS mice demonstrated significantly decreased spontaneous locomotor activity in the open field crossings ($F (5, 36) = 13.12$, $P < 0.001$) and rearings ($F (5, 44) = 9.306$, $P < 0.001$) compared to the control group. The results suggested that CUMS effectively led to decreased movement and exploration in mice. SSa or fluoxetine treatments reversed the decreased numbers of crossings and rearings with all SSa treatment groups showing at least significant difference ($P < 0.05$), fluoxetine group showing at least very significant difference ($P < 0.01$) (Figures 1C and 1D). However, there was no significant difference in number of groomings. These results revealed the potential antidepressant effects of SSa.

Tail suspension and forced swimming tests

The effects of SSa treatment on TST and FST demonstrated that CUMS mice displayed desperate behavior as indicated by increased immobility time compared to the control group ($F (5, 49) = 10.44$, $P < 0.001$) for TST (Figure 1E) and ($F (5, 46) = 7.072$, $P < 0.001$) for FST (Figure 1F]. The results suggested that CUMS led to desperate behavior in mice, while SSa or fluoxetine treatment significantly alleviated despair behavior induced by CUMS with all SSa treatments showing very high significant difference ($P < 0.001$) and fluoxetine treatment showing very significant difference ($P < 0.01$) for TST, while SSa and fluoxetine treatments demonstrated very significant difference for FST ($P < 0.01$). These results suggested that SSa played an antidepressant role by effectively improving despair behavior in mice.

qRT-PCR results

The effects of SSa or fluoxetine on mRNA expression of BDNF, TrkB, and CREB demonstrated that the mRNA expressions of tested genes were all decreased in CUMS group compared to that in the control group with $F (5, 12) = 12.81$, $P < 0.01$ for BDNF (Figure 2A), $F (5, 12) = 12.85$, $P < 0.01$ for TrkB (Figure 2B), and $F (5, 12) = 24.63$, $P < 0.05$ for CREB (Figure 2C). Administration of SSa and fluoxetine improved these genes' expressions significantly. These results showed that SSa reversed downregulation of mRNA expression of BDNF, TrkB and CREB induced by CUMS.

Western blot results

The effects of SSa administration on BDNF-TrkB-CREB signaling pathways demonstrated that CUMS mice significantly reduced BDNF levels ($F (5, 12) = 10.46$, $P < 0.01$), pTrkB/TrkB ratio ($F (5, 12) = 10.13$, $P < 0.01$), and pCREB/CREB ratio ($F (5, 12) = 12.06$, $P < 0.001$) in the hippocampus compared to controls. However, SSa and fluoxetine significantly improved BDNF (Figure 3A), pTrkB/TrkB (Figure 3B), pCREB/CREB (Figure 3C). These results suggested that SSa interfered with the downregulation of BDNF, pTrkB/TrkB, and pCREB/CREB induced by CUMS.

Discussion

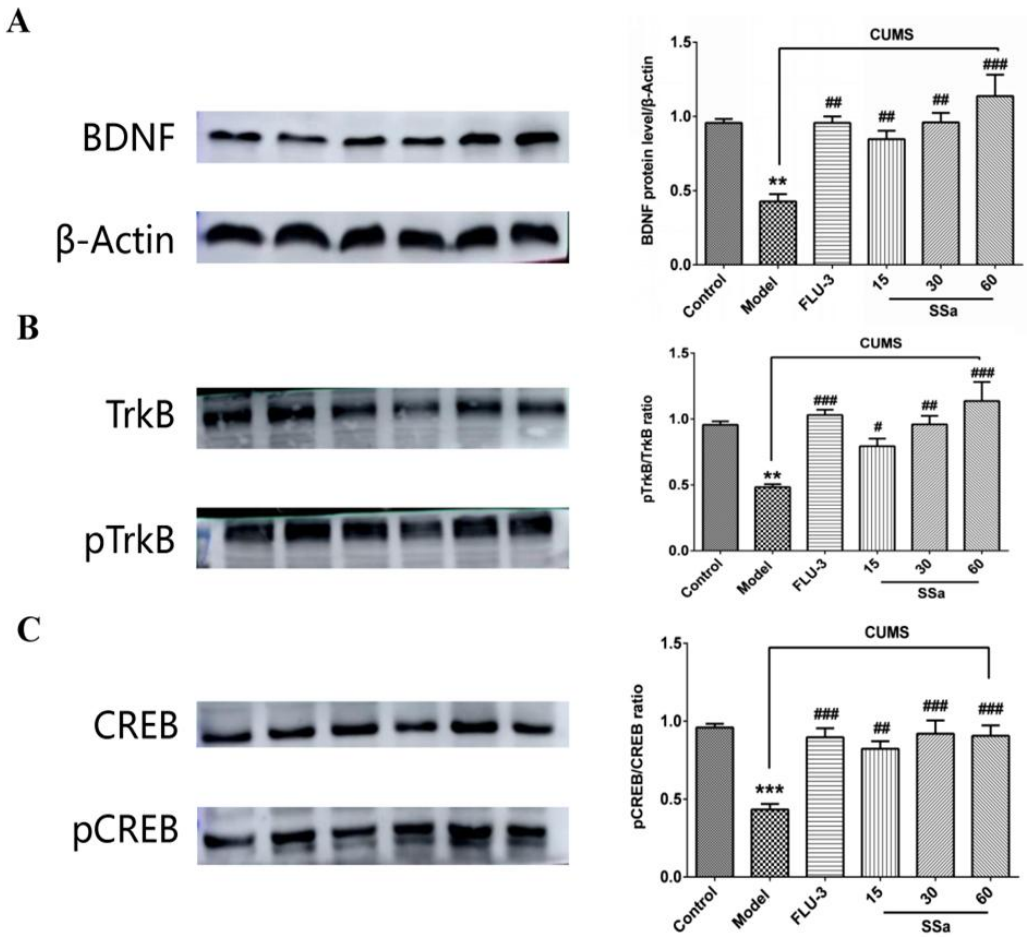


Figure 3. Protein levels of BDNF (**A**), p-TrkB/TrkB (**B**), p-CREB/CREB (**C**) in CUMS mice hippocampus. **: $P < 0.01$, ***: $P < 0.001$ *vs*. control group. #: $P < 0.05$, ##: $P < 0.01$, ###: $P < 0.001$ *vs*. model group.

Depression is a major clinical problem characterized by low mood. Clinical diagnosis of depression is primarily evaluated using the Hamilton Depression scale, and the severity of depression is judged according to the score of the depression scale. There is a lack of effective molecular diagnostic indicators for depression. It was reported that depression is primarily divided into three stages including the first stage of mild psychotic depression, the second stage of subthreshold depression that may be severe or mild, and the third stage of severe depression that is characterized by clear depression and a lack of pleasure [25]. For these three phases of depression, clinically, the primary therapeutic measures are drug therapy, psychotherapy, and physiotherapy, respectively. Traditional tricyclic antidepressants and newly marketed monoamine neurotransmitter inhibitors are the primary drugs used for depression therapy. Psychotherapy is primarily used to guide the emotions of patients, while physiotherapy is primarily electrotherapy, transcranial magnetic stimulation, and acupuncture therapy [26]. Extant medicine marketed to treat depression is divided into several subtypes including tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and selective 5-HT reuptake inhibitors (SSRIs). According to clinical investigation data, TCAs exert significant adverse effects on the cardiovascular system and has limited clinical application. MAOIs have clear toxicity and side effects including headache, nausea, insomnia, and other adverse reactions. Compared to the other two types of drugs, SSRIs are the most widely used clinically, and they

selectively inhibit the presynaptic membrane, causing 5-hydroxytryptamine (5-HT) content in the synaptic gap to increase. Fluoxetine is a representative SSRI, which has the advantages of small dose, good oral absorption, fewer adverse reactions, and good safety [27]. It is the first choice of antidepressant drugs in clinical practice. It has been reported that fluoxetine upregulates BDNF, TrkB, and CREB content in depressive model mice and plays an antidepressant role [28]. Therefore, this study selected fluoxetine as a positive control drug to evaluate the antidepressant effects of SSa [29]. Learning and memory functions of mice in CUMS depression model were altered, which might be caused by the damage to the limbic system. The hippocampus is a major part of limbic system. Previous studies reported hippocampal atrophy and axonal reduction in depressed people and in animal models of depression [30]. Therefore, this study further investigated mRNA expression levels and related proteins of BDNF-TrkB-CREB in the hippocampus of CUMS mice. This study examined the depressive-like response following administration of SSa in male Kunming mice subjected to CUMS. The results showed that administration of SSa during CUMS ameliorated depressive-like behaviors including anhedonia, weight loss, decreased spontaneous locomotor activity, and despair conditions, which might be related to the upregulation of the BDNF-TrkB-CREB pathway by regulating mRNA expression levels of BDNF, TrkB, and CREB and related protein levels of BDNF, pTrkB/TrkB, and pCREB/CREB. The results of this study laid a theoretical foundation for the development and utilization of *Radix Bupleuri*. The mechanisms of the pathway actions on depression need to be further examined in subsequent studies.

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