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Effect of liquiritin on the expression of BDNF, Bax, and Bcl-2 in the hippocampus of post-stroke depression rats

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ABSTRACT

Aims: The study intended to explore the therapeutic effect of liquiritin on PSD rats and its role in the pathogenesis of PSD.

Methods: The stroke model was established via middle cerebral artery occlusion, and the PSD model was created using chronic unpredictable mild stress combined with isolated feeding. The expressions of BDNF, Bax, and Bcl-2 proteins in the hippocampus of rats were detected using Western blot and immunofluorescence staining after 6 weeks of modeling.

Results: The weight, sucrose consumption and activity of the PSD rats decreased ($P < 0.05$) compared with the normal control and stroke groups. On the contrary, the weights of the liquiritin and escitalopram groups increased and their sucrose consumption and activity increased in the open-field test ($P < 0.05$) compared with the PSD and normal saline (NS) groups.The result of immunofluorescence staining and western-blot showed that BDNF and Bcl-2 increased in the liquiritin group and Bax increased significantly in the stroke and PSD groups ($P < 0.05$).

Conclusions: Liquiritin is capable of inhibiting neuronal apoptosis in the hippocampus of PSD rats to improve depression symptoms. This improvement may be achieved by reducing the expression of Bax and increasing the expressions of Bcl-2 and BDNF in the hippocampus of PSD rats.

Introduction

Stroke is a leading cause of death in developing countries [1,2]. Striking quality, post-stroke depression (PSD) is the most common complication after stroke, which severely impacts >30 % of stroke survivors [3]. PSD affects the daily life and influence the quality of life, psychological cognition and social function of the survivors in different degrees [4]. Most conventional antidepressants interfere the normal biological processes and may lead to brain damage. Many serious adverse effects of antidepressants have been identified, and the most important of that being sexual dysfunction and withdrawal reactions [5]. It is imperative to explore the pathogenesis and seek novel treatment measures of PSD.

Apoptosis occurs during the process of brain tissue injury and it's one of the key pathophysiological processes of cerebral ischemia and depression [6,7] . Bcl-2 is inhibiting the apoptosis and Bcl2- associated X protein (Bax) is promoting the apoptosis [8]. Studies have reported that intrinsic mitochondrial death plays an essential role in regulating the apoptosis [9,10]. And the Bcl-2 family of proteins were involved in the internal pathway of mitochondrial apoptosis. The Bcl-2/Bax ratio is an important index of apoptosis. Brain-derived neurotrophic factor (BDNF), which is distributed widely in the cerebral cortex, hippocampus and striatum, is associated with the neuroplasticity processes and plays a critical role in the mechanism of depression [11] . Our previous studies have demonstrated that there is an immense drop in BDNF in the depressed model rats [12,13].

The hippocampus is essential for learning, memory, and cognition, and the dentate gyrus (DG) dysfunction is a critical factor in depressive disorder [14,15]. The hippocampus can generate new neurons and contributes to functional plasticity in pathological condition.

Licorice root, a traditional herbal medicine, has been used widely in China. The major bioactive compounds of licorice root including

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liquiritin, glabridin and isoliquiritigenin [16]. Liquiritin exerts neuroprotective and neurotrophic effects on the hippocampal cells and has been shown to have an antidepressant-like effect [17,18]. Recent studies have shown that liquiritin reduced inflammation and apoptosis via regulating AMPKα2 dependent signaling pathway, and liquiritin treatment inhibited inflammatory cell migration, suppressed cardiac apoptosis [19]. However, there are few literature reports on whether liquiritin exerts a positive effect on PSD. Hence, this study intended to explore the expressions of BDNF, Bcl-2 and Bax in the hippocampus of PSD rats after liquiritin treatment and to provide a theoretical basis for the clinical development of liquiritin therapy for PSD.

Materials and methods

Animals

Adult female Sprague–Dawley (SD) rats (weight: 250 ± 50 g) were obtained from the Experimental Animal Center of Dali University. The rats were housed in breeding cages (maximum 5 rats per cage) at 22 ± 2 °C under 55 ± 4 % humidity and a 12-h/12-h light/dark cycle. We attempted our best to reduce the suffering of animals. Liquiritin (purity >97 %) was purchased from Hubei Xinyuanshun Pharmaceutical and Chemical Co., Ltd; escitalopram was purchased from H.Lundbeck A/S.

Animal model establishment and grouping

Initially, all rats were fed a normal diet and drinking water over 7 days for acclimatization. Then, 13 rats were randomly assigned to the normal control group, and up to 5 rats per cage. The other rats were used to trigger a focal cerebral ischemia rat model by the middle cerebral artery occlusion (MCAO). The rats' limbs were fixed in the supine position and then anesthetized. An incision was created in the neck to expose the blood vessels on the left side of the neck, followed by careful separation of the external and internal carotid arteries. The monofilament nylon was inserted into the internal carotid artery and gently pushed forward by approximately 19 mm to block the blood flow of the left middle cerebral artery for 60 min. Eventually, the left cervical incision was sutured and disinfected. The neurological function score was recorded at the appropriate time, the successful stroke model rats were accepted. After the surgery, the rats were fed separately in avoidance of outside interference. Finally, the successful stroke model rats were randomly assigned to the stroke group, PSD group, escitalopram group, liquiritin group, and normal saline group according to the intervention drugs, $n = 13$/group.

Chronic unpredictable mild stress

Two weeks after the stroke model was established, all rats except the normal control group and stroke group were single cage feeding for 1 week and then subjected to chronic unpredictable mild stress (CUMS) [20]. According to a previously reported method, the rats were exposed to 1 of the 8 stressors randomly everyday for 3 weeks, the stressors following (1) food deprivation for 24 h, (2) water deprivation for 24 h, (3) light and dark cycle (12 h for 1 cycle), (4) 80-dB noise stimulation for 12 h, (5) 4 °C swimming for 5–10 min, (6) tail pinching for 1–2 min, (7) 24-h in a wet cage, and (8) physical immobilization for 2 h. The animals were treated CUMS subjected to 1 of these stressors every day [21].

On the 21st day of inducing CUMS, the rats separately received normal saline, liquiritin, and escitalopram, except for the normal control, stroke, and PSD groups. The dosage of normal saline, liquiritin, and escitalopram was kept at 10 mL/Kg in deionized water. All groups' rats were scored at the same time, once a day for 3 weeks.

Behavioral tests

Sucrose preference test (SPT) and open-field test (OFT) activities were evaluated after inducing CUMS. The weights of the animals were determined weekly.

The SPT was used to assess animals' anhedonia after suffering CUMS. Before the SPT, all rats were allowed access to 2 bottles of 1 % sucrose solution. After 2 days of habituation, the rats were provided one bottle of the 1 % sucrose solution and one bottle of pure water for 24 h. Then, the rats were deprived of water for 24 h. In order to eliminate any directional preferences, the positions of the two bottles in each group were switched randomly throughout the experiment. The bottles were then removed and weighed after 24 h and measured for the extent of sucrose consumption.

The OFT was applied to evaluate the animals' basal activity. The test was based on the same methodology as reported previously, albeit with some minor changes [12]. The OFT apparatus included a wooden box (1 × 1 m) with black walls of 50-cm height. The white floor was uniformly divided with black lines into 40 squares of equal area. The test was conducted in a quiet environment, and the rats were allowed to move free in the box. The movements of all animals were quantified by counting the number of crossings (≥3 paws in one square) and the number of standing on hind legs for 5 min. The testing chamber was cleaned with 75 % alcohol after each test.

Organizational process

The rats in all groups anesthetized with 3.6 % chloral hydrate (1 mL/100 mg). All groups rats' brain were removed at the 6th week after the model established. The collected brains were rapidly dissected and the hippocampus was washed with 4 °C pre-cooled DEPC treated water to remove all bloodstains. The hippocampus was then stored at –80 °C refrigerator until further use. For immunofluorescence staining, the rats were in turn transcardially perfused with normal saline, phosphate-buffered saline (PBS), and then fixed with 4 % paraformaldehyde (PFA). The hippocampus was cut from the brain and soaked in 20 % sucrose solution for 48 h at 4 °C in a refrigerator to let it sink to the bottom and then embedded in paraffin. We used a microtome to cut coronal consecutive sections of thickness 3–5 μm.

Immunofluorescence staining

The expressions of BDNF, Bax, and Bcl-2 in the hippocampus were discovered by immunofluorescence staining. The cells with red fluorescence in the immunofluorescence experiment implied positive. The primary antibody including BDNF (1:500, Abcam Inc), Bax (1:300, Abcam Inc), and bcl-2 (1:100, Abcam Inc) were added to the brain slice separately and incubated overnight in the refrigerator at 4 °C. The next day, the secondary antibody (Sheep anti-rabbit IgG 1:100, KPL company) was added to brain slices at room temperature for 1 h and then the slices were washed thrice with PBS. The slices were then immediately observed by laser confocal microscopy after the addition of glycerol dropwise to seal the film. Five discontinuous sections were selected from each rat, and the experimental results were expressed by counting the positive cells.

Western blotting

Western blotting analysis detected the quantitative expression of BDNF, Bax, and bcl-2 protein in the hippocampus. The hippocampal tissue cryopreserved at –80 °C was lysed for 30 min, and the lysate was centrifuged at 1500 rpm for 15 min (centrifugal radius = 16 cm) to obtain the supernatant. The protein concentrations of the supernatant were measured by BCA protein assay kit (Boster, China). The supernatant protein samples were subjected to Biss-Tris gel electrophoresis and then transferred to the polyvinylidene fluoride (PVDF) membranes and blocked with 5 % skim milk for 2 h. Then, the membranes were treated with β-actin (1:500, Cell Signaling Technology), and next added BDNF (1:500, Abcam Inc.), Bax (1:1000, Abcam Inc.), and Bcl-2 (1:1000,

Abcam Inc.) separately at 4 °C overnight. The next day, the PVDF membranes were washed thrice with TBS for 5 min and then incubated with a secondary antibody (1:500, Cell Signaling Technology) at room temperature for 2 h. The GE ImageQuant LAS 4000 ultra-sensitive chemiluminescence imager was used for imaging. The relative optical densities were finally calculated.

Statistical analyses

All results were analyzed by SPSS v. 20.0 statistical package and presented as the mean ±*S*.E.M. The measurement data were expressed in $X \pm s$ and analyzed by one-way analysis of variance (ANOVA). We applied the least significant difference (LSD) test for pairwise comparison between the groups, $P < 0.05$ was considered to indicate statistical significance.

Results

Behavioral indexes

Six weeks after modeling, the weight of the PSD rats and NS group rats diminished considerably compared with the normal control group and stroke group ($P < 0.05$). Compared with the PSD group and NS group rats, those receiving escitalopram and liquiritin rats presented significantly increased body weight ($P < 0.05$). Sharp reduction in sucrose consumption was noticed in the PSD group and NS group rats compared with the other group rats ($P < 0.05$). The PSD group and NS group rats lacked pleasure and showed a reduction in spontaneous horizontal activities compared with the other groups in the OFT ($P < 0.05$). The vertical movement of the rats treated with escitalopram and liquiritin were essentially higher than those of the PSD group and NS group ($P < 0.05$)(Fig. 1).

Immunofluorescence analysis

The positive cells for BDNF, Bax, and Bcl-2 were observed in the hippocampus using a confocal microscope (ZEISS; LSM 710; Germany) with red fluorescence. The results of immunofluorescence staining showed that the number of Bcl-2 positive neurons were significantly higher in the liquiritin, escitalopram and normal control groups than that in the PSD, stroke, and NS groups ($P < 0.05$). Compared with the normal control and liquiritin groups, there was an increase in the number of hippocampus Bax-positive neurons in the PSD, stroke, and NS groups ($P < 0.05$). The number of BDNF positive neurons were significantly higher in the liquiritin group than that in the stroke,PSD, and NS groups ($P < 0.05$). Furthermore, the difference between the liquiritin and escitalopram groups was not statistically significant in the expressions of BDNF, Bcl-2 and bax ($P < 0.05$) (Fig. 2).

Western-blot analysis

Western-blot results showed that the relative optical densities of BDNF and Bcl-2 decreased significantly but that of Bax increased significantly in the stroke, PSD, and NS groups ($P < 0.05$). However, there was no difference in the other groups ($P > 0.05$) (Fig. 3).

Discussion

The present study investigated whether liquiritin has a potentially protective effect on PSD rat model. To figure out the effect of liquiritin on PSD rats, we performed SPT, OFT and weighed the rats. The results showed that the weight of the PSD rats increased and the sucrose consumption added also the activity improved in the OFT after the treatment with liquiritin and escitalopram. Several studies in related fields have clearly demonstrated that liquiritin improves the depressive symptoms in rats [17,18,22], which consistent with our findings.

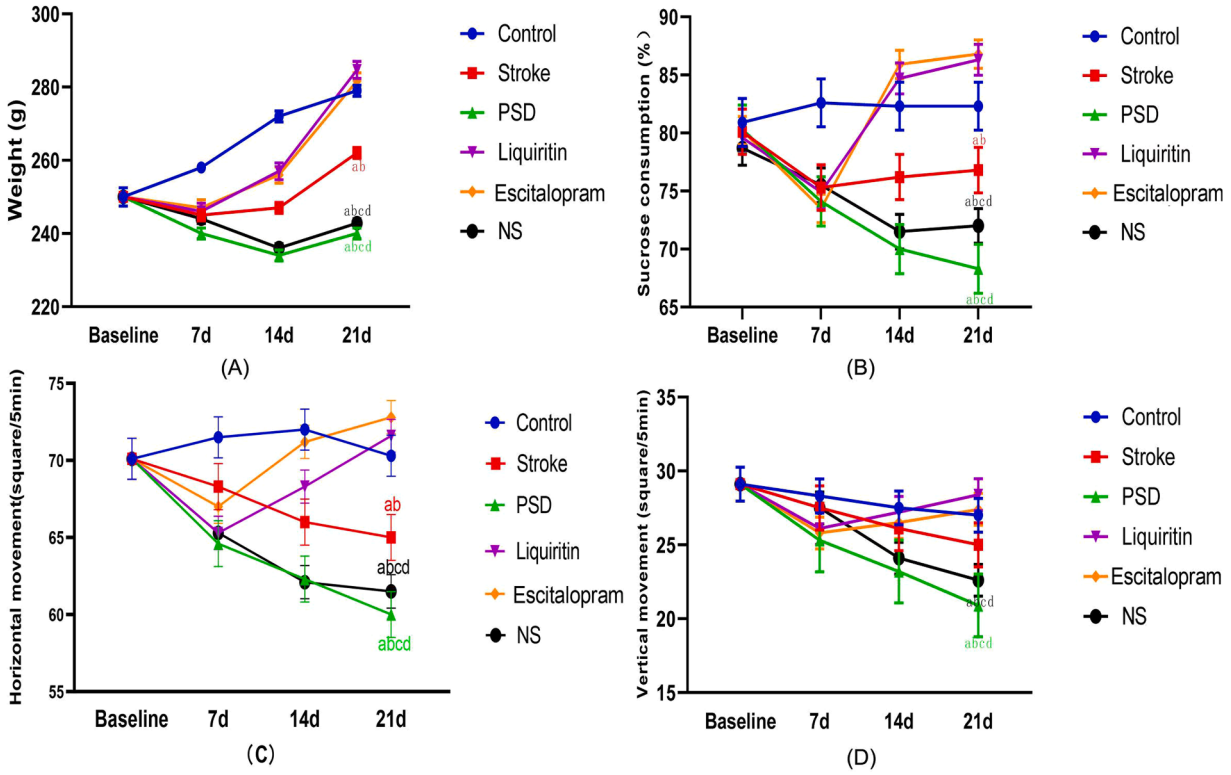

Fig. 1. The comparison of behavioral tests among all rat groups after CUMS. (A) bodyweight, (B) sucrose consumption, (C) horizontal movement, and (D) vertical movement. [a]$P < 0.05$, compared with the liquiritin group; [b]$P < 0.05$, compared with the escitalopram group; [c]$P < 0.05$, compared with the normal control group; [d]$P < 0.05$, compared with the stroke group.

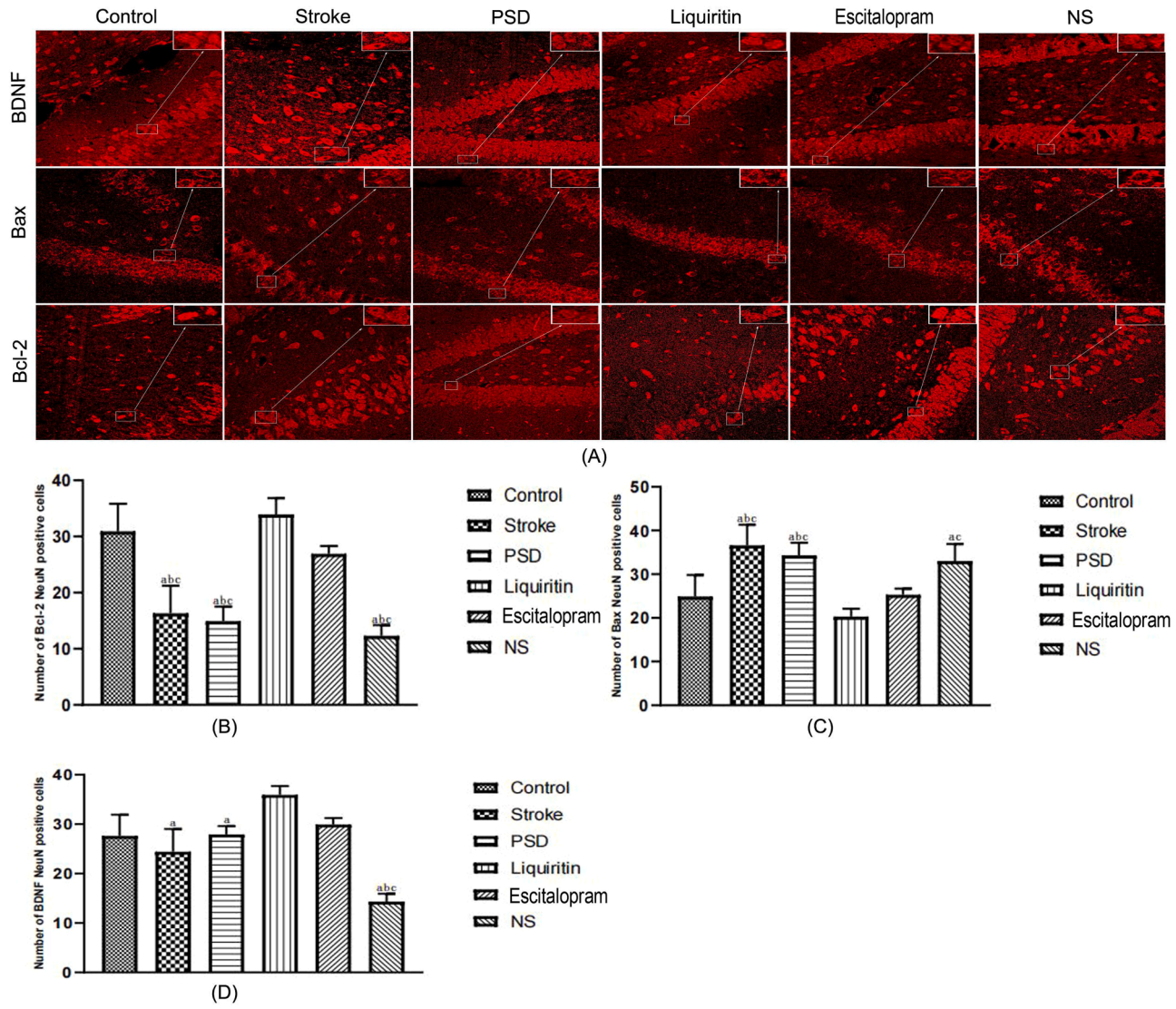

Fig. 2. Immunofluorescence detection of the BDNF, Bax, and Bcl-2 expression of rats in each group. (A) BDNF, Bax, and Bcl-2 expression (red fluorescence) in the hippocampus. (Scale bar = 25 μm) Histograms showing (B/C/D) the number of Bcl-2 and Bax, BDNF positive cells in the hippocampus of each group. $^{a}P < 0.05$, compared with the liquiritin group; $^{b}P < 0.05$, compared with the escitalopram group; $^{c}P < 0.05$, compared with the normal control group.

Western blotting and immunofluorescence staining experiments revealed the expressions of BDNF, Bax and Bcl-2 in the hippocampus of PSD rats. The obtained results showed that liquiritin exerted antidepressant-like effects via up-regulating the expression of BDNF and Bcl-2 and at the same time down-regulating the expression of Bax in hippocampus.

PSD is closely associated with increased mortality in stroke survivors. The mechanism of PSD remains unclear. Previous research had shown that the mechanisms of PSD may be including the psychosocial and biological factors, which comprising the ischemic position, inflammatory system activation, genetic predisposition, neuronal cell apoptosis, BDNF, and the hypothalamic–pituitary–adrenal axis' activation. BDNF is the most bountiful neurotrophin which broadly dispersed in the brain and it involved in the recuperation of capacities after stroke. The PSD rats exhibited symptoms similar to those of patients with depression, such as nerve injury, decreased activity, loss of pleasure, and weight loss [23]. The present animal model provides a method to study the pathogenesis of PSD and may offer theoretical support for the discovery of new antidepressant drugs. Previous studies have revealed that the volume of the hippocampus in patients with depression is smaller than that in normal people, which indicates the hippocampus is closely associated with the occurrence of depression [24–26]. Studies have suggested that antidepressants improve depression-like behavior by promoting hippocampal neurogenesis and reducing apoptosis [27–29], so we chose the rat hippocampus as the study site. Apoptosis is controlled by proapoptotic family members (Bax) and antiapoptotic family members (Bcl-2). The Bcl-2/Bax index decreased may cause the loss of matrix metalloproteinase and raise the mitochondrial membrane permeability and finally led to apoptosis [30]. Furthermore, BDNF plays a significant role in the pathogenesis of depression and it's critical for the growth and differentiation of the nervous system after stroke. Researchers have identified that the occurrence of PSD is closely related to the decrease in BDNF content in the brain, especially in the hippocampus [13,31]. BDNF in the DG (one of the subfields of the hippocampus) adjusting the morphology and electrical activity of neurons, thereby altering the excitability of the cerebral cortex [32,33]. We demonstrated that the number of Bcl-2 positive neurons and BDNF positive neurons were increased and Bax-positive neurons were decreased in liquiritin group, which means liquiritin can up-regulate the expressions of BDNF and Bcl-2 and reduce Bax in hippocampus, so we inferred that liquiritin inhibits apoptosis through adjusting the level of the BDNF and anti- and pro-apoptotic proteins.

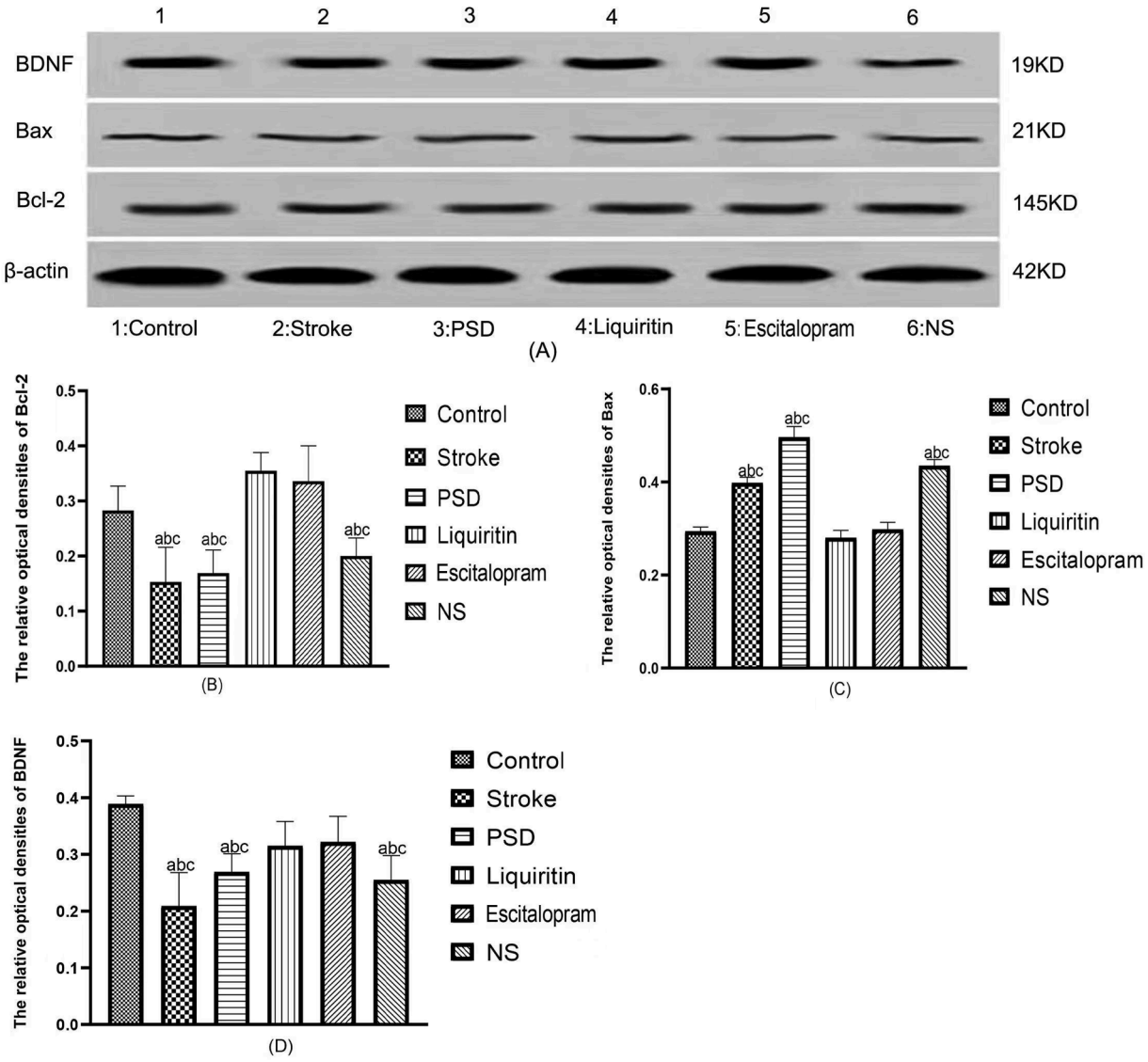

Fig. 3. The expression of Bax, Bcl-2, and BDNF proteins of different model groups at the 6th week of CUMS. (A) Western blotting revealed the Bax, Bcl-2, and BDNF expression levels in the hippocampus. β-actin was used as a gel loading control. The histograms show (B/C/D) the relative optical densities of Bcl-2, Bax, and BDNF in the hippocampus of each group. $^{a}P < 0.05$, compared with the liquiritin group; $^{b}P < 0.05$, compared with the escitalopram group; $^{c}P < 0.05$, compared with the normal control group.

Liquiritin (7-hydroxy-2-[4-[3,4,5-trihydroxy-6-(hydroxymethyl) oxan-2-yl] oxyphenyl]-chroman-4-one, 1) is one of the Chinese herbal medicines for relieving depression and is an active component of Glycyrrhiza uralensis Fisch. Liquiritin possesses a wide range of pharmacological activities such as anti-aging, anti-apoptotic, anti-inflammation, anti-radiation, anti-depression, and neuroprotection [34,35]. It has been reported that liquiritin significantly reduced the ratio of 5-HIAA/5-HT in the hippocampus, hypothalamus and cortex, and the mechanism of liquiritin produced significant antidepressant-like effects may be due to increased 5-HT and NE in the mouse hippocampus, hypothalamus and cortex [17]. In this study, the intraperitoneal perfusion of liquiritin or escitalopram up-regulated the expression of BDNF and Bcl-2 proteins in the PSD rats, whereas the expression of the pro-apoptotic factor Bax was reduced. Our behavioral score showed that the symptoms of depression were significantly improved after the rats received liquiritin or escitalopram. These findings suggest that liquiritin and escitalopram through adjusting the expressions of BDNF, Bax, and Bcl-2 proteins in rat hippocampus may alleviate PSD symptoms.

A meta-analysis has shown that the clinical effects of escitalopram are similar to those of other selective serotonin reuptake inhibitors (SSRIs) [36]. The escitalopram have better therapeutic effect than other SSRIs [37]. Escitalopram may improve poststroke symptoms by increasing the levels of BDNF, neural cell migration, neurogenesis and microvessel support after ischemic stroke [38]. The results of the present study indicate that the efficacy of liquiritin is similar to escitalopram. Nevertheless, some studies showed that escitalopram represented gastrointestinal side effect [39], sexual dysfunction [40], rhabdomyolysis [41], and other adverse effects, so it's necessary to find an alternative medicine for escitalopram.

In conclusion, liquiritin may improve the PSD symptoms by enhancing the expressions of BDNF and Bcl-2 in the hippocampus meanwhile reducing the expression of Bax protein thus inhibiting hippocampal neuronal apoptosis, promoting neuronal survival, and improving neural synaptic plasticity. The results are likely to provide a preliminary basis for further research on the clinical application of liquiritin.

CRediT authorship contribution statement

Gui-Liu Yan: Writing – original draft, Software. **Dan Dai:** Writing –

original draft, Project administration. **Qiang Zi:** Software, Investigation. **Fu-Mei Zhang:** Supervision, Formal analysis. **Yun Li:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Statements and declarations

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