Original Article

Behavioral defects induced by chronic social defeat stress are protected by *Momordica charantia* polysaccharides via attenuation of JNK3/PI3K/AKT neuroinflammatory pathway

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Background: The aim of this study was to evaluate the protective effects of *Momordica charantia* polysaccharides (MCP) on depressive-like behaviors.

Methods: The chronic social defeat stress (CSDS) mice model was used to evaluate the effects of MCP and their underlying mechanisms. Social interaction test (SIT), sucrose preference test (SPT), and tail suspension test (TST) were performed for behavioral assessments. Expression levels of inflammation mediators and phosphatidylinositol 3-kinase (PI3K) activity were determined using commercial ELISA kits. The expression of key proteins in the c-Jun N-terminal protein kinase (JNK3)/PI3K/protein kinase B (AKT) pathway were measured using western blot and RT-PCR.

Results: The results showed that chronic administration of MCP (100, 200, 400 mg/kg/day) significantly prevented depressive-like behaviors in CSDS mice as assessed by SIT, TST and SPT. Elevated levels of proinflammatory cytokines [tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β)], and expression of JNK3, c-Jun, P-110β proteins were observed in the hippocampus of CSDS mice. Moreover, the activity of PI3K and phosphorylation level of AKT were reduced in the hippocampus of CSDS mice. Interestingly, the administration of MCP reversed these changes. Furthermore, the protective effects of MCP on CSDS mice were partly inhibited by the PI3K inhibitor, LY294002.

Conclusions: In conclusion, the protective effects of MCP against depressive-like behaviors in CSDS mice might be due to a reduction in neuroinflammation and the down-regulation of the JNK3/PI3K/AKT pathway in the hippocampus.

Keywords: *Momordica charantia* polysaccharides (MCP); depressive behaviors; neuroinflammation; c-Jun N-terminal protein kinase (JNK3)

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Introduction

Depression is characterized by change in mood, such as feeling guilty, low self-worth, low energy and loss of interest or pleasure. Depression has been recognized as a globally prevalent psychiatric disorder according to the World Health Organization (1) owing to resistance to treatment and high risk of suicide. The commonly prescribed medicines have certain drawbacks, including a low curative ratio, limited spectrum of activity, slow onset of action and excessive side effects (2). Therefore, it is necessary to explore new antidepressants, which enable clinicians to diversify their treatment options.

Multiple clinical studies have shown that the mean levels of proinflammatory cytokines are elevated in the blood of depressed individuals. Many pro-inflammatory factors, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β), play an important role in the pathophysiological process of depression (3,4). In animal studies, researchers reported that depressed animals exhibit higher levels of pro-inflammatory cytokines (5) which might inhibit neurotransmission and plasticity, and suppress neurogenesis (6). Therefore, inflammation might be an important biological mechanism for depression. There are several signaling pathways involved in neurodegenerative pathology and mood diseases related to inflammation, such as the C-Jun N-terminal protein kinase (JNK) pathway.

JNK, a member of the mitogen-activated protein (MAP) kinases, consists of at least 10 JNK isoforms, which are encoded by three genes: *Jnk1*, *Jnk2*, *Jnk3* (7). Altered distribution and activation of JNK3 in post-mortem brain sections suggests that JNK3 is involved in Alzheimer's disease (8,9). Furthermore, stress-induced activation of JNK in the hippocampus is associated with emotional memories deficits, which can be improved by the administration of JNK inhibitors (10,11). Additionally, treatments with JNK inhibitors prevent the impairment of conditioned fear, indicating that JNK activity plays an important role in stress-impaired fear conditioning (12). Signal stressors delay the loss of apical dendrites and increase the number of basal dendritic trees (13), which elevates phosphorylation and activity of JNK in hippocampal sub-regions (12). JNK3 is abundantly expressed in the brain and functions as an essential player in the neuronal stress response in various neuropathological diseases, however, the underlying mechanisms differentially regulating JNK3 in depression remain unclear (14,15).

As a downstream target of JNK3, the protein p110 beta (P-110 β) is involved in the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway. The activity of PI3K and phosphorylation of AKT is higher in the hippocampus of *Jnk3* mull mice (16). Evidence suggests that the PI3K/AKT pathway is involved in the pathophysiology of depression. Some antidepressant-like compounds target this pathway as well, which is involved in synaptic neurotransmission, neuronal cell proliferation, migration and plasticity (17-19). Specifically, AKT2 plays an important role in the process of neuronal differentiation, survival, and dopamine transporter cell surface expression (20,21). Furthermore, studies show that deficiency of AKT2 is associated with depressive-like behaviors in mice (22).

Momordica charantia (MC) is a popular vegetable and is consumed as food-medicine in traditional Chinese medicine. The polysaccharide of MC is one of the major active ingredients and contributors to the beneficial effects of MC (23,24). Studies suggest that *Momordica charantia* polysaccharide (MCP) possesses various beneficial effects, including antioxidant and anti-inflammatory responses, which are involved in the pathophysiology of depression (25,26). However, whether MCP contributes to neuroprotective effects against depressive-like behaviors induced by chronic social stress is still unknown. We hypothesize that MCP protects against depressive-like behaviors and decreases the expression of proinflammatory cytokines through the JNK3/PI3K/AKT signaling pathway in the chronic social defeat stress (CSDS) depressed animal model.

Methods

Animals

The 8-week-old male C57 mice (Experimental Animal Center of China Three Gorges University) were 8–10 weeks of age, the room temperature was 24±1 ℃, and relative humidity was 55%±10% with 12-h light/dark cycle. After 1 week, in compliance with the National Institute of Health and the Animal Care, Inspection by members in The Medical Animal Care & Welfare Committee of Three Gorges University, the behavioral experiments were performed.

Drug preparation and administration

The preparation of MCP was described as previous publication (26). The MC was purchased from a local

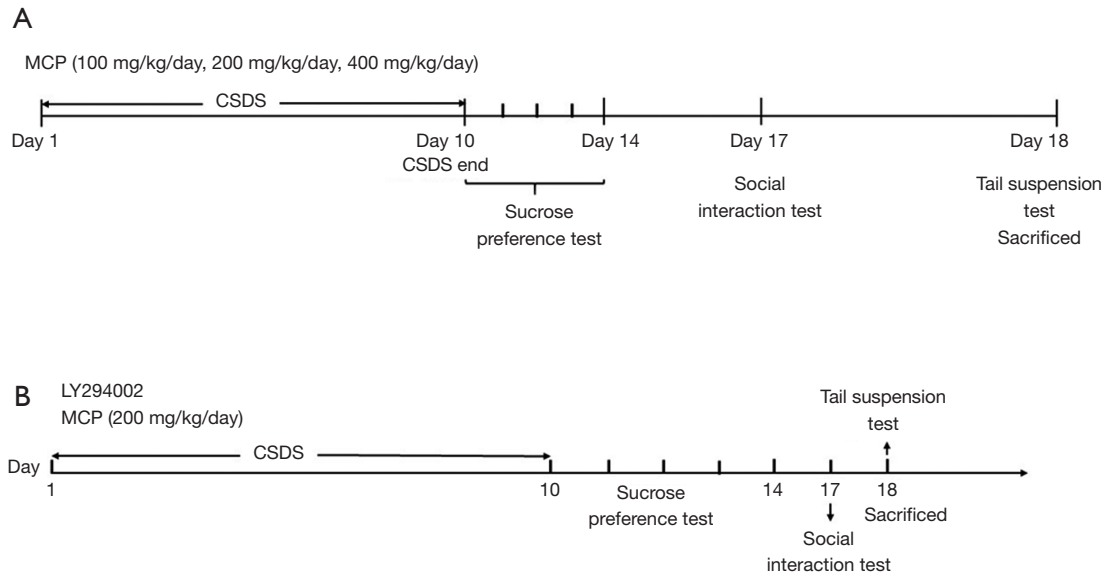

Figure 1 Schematic timeline of the experimental procedure. (A) CSDS mice were treated with MCP; (B) CSDS mice were treated with MCP and LY294002. MCP, Momordica charantia polysaccharides; CSDS, chronic social defeat stress.

vegetable market in Yichang City of Hubei Province. Briefly, water extraction and alcohol precipitation were used to extract MCP from *M. charantia*. MCP was dissolved in distilled water.

LY294002 (Sigma Chemical, St Louis, MO, USA), a phosphatidylinositol-3-kinase (PI3-K) inhibitor, was administered via direct intraperitoneal injection (i.p.) 30 min after stress. Animals received LY294002 at a dose of 7.5 mg/kg, dissolved in dimethyl sulfoxide (DMSO) to a volume of 10 μL per gram of body weight.

Experimental design

The CSDS mice model was established based on our previous study (27). The schematic timeline of the experimental procedures was shown in *Figure 1*. After establishment of CSDS model, the behavioral tests were performed.

Social interaction test (SIT)

A two-trial SIT was described previously (28). Briefly, there are two trials ("target absent" trial, "target present" trial) in this test, the time was last for 5 minutes in every trial. In the first trial, the behaviors of experimental C57 mouse were free in a 44 cm × 44 cm square-shaped open-field arena, which possessed a 10 cm × 6 cm wire-mesh cage opposed to one side. In the second trial, the target (an unfamiliar CD1 retired breeder mouse) was reintroduced into this arena. During the 5 minutes, the interaction time between the test C57 mouse and CD1 mouse in the interaction zone was recorded.

Sucrose preference test (SPT)

The SPT was carried out in 4 days. At first, pure water and 1% sucrose solution were supplied to the test mouse in 2 days, respectively. Then, the food and two bottles were both deprived in next 18 hours. The last day, the test was performed. The weights of two bottles were measured before and after the test.

Tail suspension test (TST)

This test was performed according to previous study (29). C57 mouse was individually suspended by adhesive tap (1 cm from the tail tip) 60 cm above the floor. The total test time was 6 minutes. The mouse was considered immobile only when it was hanging passively and completely motionless. The immobility time was recorded with a video camera. The recorder started to record the time and ended when the mouse mice to mobile. At the end of the test, the

immobility time was accumulated. The observer who performed the TST test was unaware of animal grouping and treated each mouse equally.

PI3K activity assay

The bilateral hippocampus of sacrificed test mice was dissected. The hippocampus proteins were collected in NP-40 lysis buffer (Servicebio, Wuhan, China). After the lysis centrifuged (12,000 ×g, 15 minutes, 4 ℃), collecting the supernatants. According to the manufacturer's guidelines, PI3 Kinase assay kit (Echelon Biosciences, USA, catalog number: K-1000s) was used to determined PI3K activity.

Determination of proinflammatory cytokines

Commercially-available kits (R&D System, USA) were used to assay the concentrations of TNF-α (R&D System, USA, catalog number: MTA00B), IL-6 (R&D System, USA, catalog number: M6000B) and IL-1β (R&D System, USA, catalog number: MLB00C), which were expressed as pg/mL protein. The protein levels of tissue supernatant were estimated.

RT-PCR

The bilateral hippocampus of sacrificed test mice was dissected. The hippocampus total RNA was collected by isolated with the use of Trizol reagent (Invitrogen, San Diego, CA, USA). Then, total RNA (1 mg) was reverse transcribed, and the resulting cDNA (1 mL) was used to detect the transcripts. The primers used for *pik3cb* and GAPDH (Invitrogen) were:

pik3cb: forward 5'-CTATGGCAGACAACCTTGACAT-3', reverse 5'-CTTCCCGAGGTACTTCCAACT-3',

GAPDH: forward 5'-ACATTGTTG CCATCA ACGAC-3', reverse 5'-ACGCCAGTAGACTCCACGAC-3'.

Western blot

The bilateral hippocampus of sacrificed test mice was dissected. The hippocampus proteins were collected in RIPA buffer (Servicebio). After the lysis centrifuged (12,000 ×g, 15 minutes, 4 ℃), collecting the supernatants. The quantified samples were loaded and separated by 8–12% SDS-PAGE gels and then transferred to PVDF membrane (0.45 μL, Millipore, USA). Membranes were blocked with 5% non-fat milk in TBST at room temperature for 1 h and then incubated with P110 β (Cell Signaling Technology, USA, catalog: 3011), JNK3 (Cell Signaling Technology, USA, catalog: 2305), c-Jun (Cell Signaling Technology, USA, catalog: 9165), phospho-AKT (Ser473) (Cell Signaling Technology, USA, catalog: 4060), total AKT (Cell Signaling Technology, USA, catalog: 4691), and β-actin (Cell Signaling Technology, USA, catalog: 3700) at 4 ℃ overnight. The membranes were incubated with a horseradish peroxidase-conjugated anti-rabbit or anti-mouse secondary antibody (1:3,000, Servicebio) at room temperature for 2 h. Bands were visualized with enhanced chemiluminescence (Clinx Science Instruments Co. China).

Statistical analysis

The data were showed as means ± SEM. The analysis was performed by the SPSS 13.0 software. The comparisons between groups were performed using one-way analysis of variance (ANOVA) followed by post hoc LSD test. $P<0.05$ was considered as statistically significant.

Results

MCP prevents depressive-like behaviors caused by CSDS

We examined the protective effects of MCP in the CSDS mouse model. The schematic timeline of the experimental procedures is shown in *Figure 1*. MCP was administered daily by gavage (at doses of 100, 200 and 400 mg/kg) 30 minutes before stress was induced. The behavioral tests suggested that there was a decrease in the interaction time of CSDS mice in SIT, and an increase in the immobility time in TST, compared to control mice. Furthermore, there was a reduction in sucrose preference in SPT (*Figure 2*). However, CSDS mice administered 200 and 400 mg/kg/day of MCP exhibited obvious improvements in their behavioral indexes.

MCP decreases the levels of proinflammatory cytokines

To explore the protective mechanisms of MCP, the levels of TNF-α, IL-6, and IL-1β in the hippocampus were analyzed. The levels of these pro-inflammatory cytokines were significantly higher in CSDS mice compared to the control group. However, administration of MCP decreased the levels of TNF-α, IL-6, and IL-1β in the hippocampus of CSDS mice (*Figure 3*).

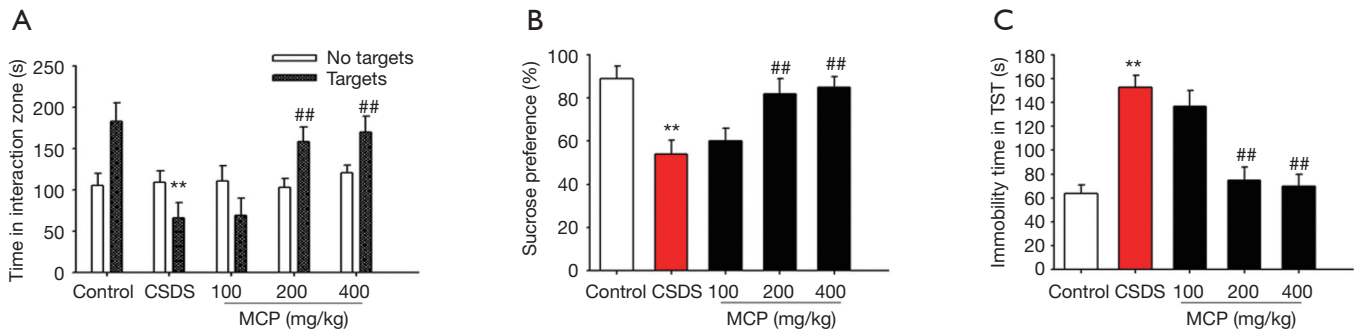

Figure 2 The antidepressant effects of MCP on the social interaction test (SIT), sucrose preference test (SPT) and tail suspension test (TST) with different concentrations. (A) SIT; (B) SPT; and (C) TST. The data are expressed as means ± SEM (n=10); **, P<0.01 compared to control; ##, P<0.01 compared to CSDS group. MCP, Momordica charantia polysaccharides; CSDS, chronic social defeat stress.

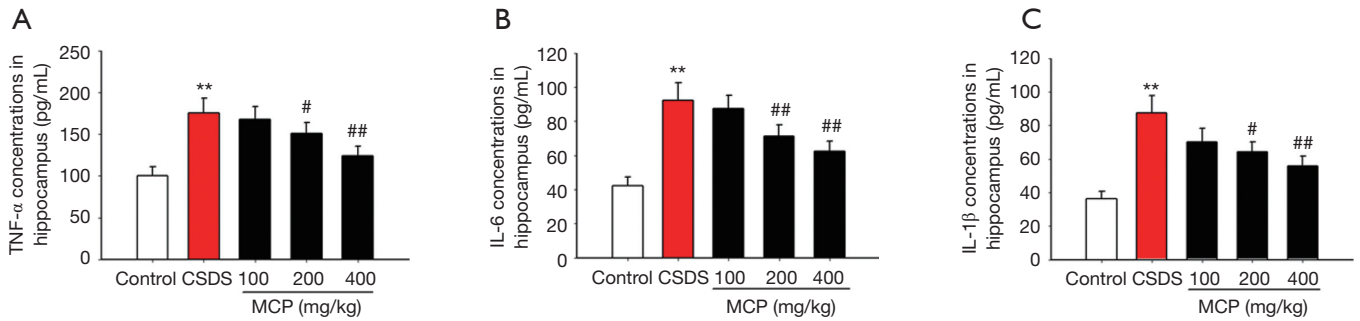

Figure 3 Effect of MCP on the concentration of proinflammatory cytokines TNF-α, IL-6, and IL-β. (A) TNF-α; (B) IL-6; and (C) IL-β. The data are expressed as means ± SEM (n=10); **, P<0.01 compared to control; #, P<0.05, ##, P<0.01 compared to CSDS group. MCP, Momordica charantia polysaccharides; CSDS, chronic social defeat stress.

MCP inhibits JNK3 and c-Jun expression in the hippocampus of CSDS mice

The JNK pathway is a critical cellular signaling pathway and a target of anti-inflammation therapies for neuroprotection (29). Studies show that MCP significantly suppresses the activation of JNK3 in ischemia-reperfused brains (30). Protein expression levels of JNK3/c-Jun and AKT were analyzed using western blot. PI3K activity was also assayed (*Figure 4*). It was observed that the expression of JNK3, c-Jun and p110 β proteins were higher in CSDS mice than in control mice. However, the activity of PI3K, mRNA expression of *pik3cb*, and protein expression of phosphorylated AKT had decreased. Administration of MCP at a concentration of 200 mg/kg/day partially reversed the above observations.

MCP protects against the depressive-like behaviors of CSDS mice through the JNK3/PI3K/AKT pathway

We observed that LY294002 (a PI3K inhibitor) partly abolished the antidepressant-like effects of MCP (*Figure 5*). The protective effects of MCP on SPT, SIT and TST were partly reversed by LY294002. The decrease in TNF-α, IL-6, and IL-1β expression levels in the hippocampus of CSDS mice after MCP administration were inhibited by LY294002 (*Figure 6*). Furthermore, compared to administration of MCP, the administration of LY294002 reduced the protein expression levels of phosphorylated AKT, inhibited PI3K activity and mRNA expression of *pik3cb*, and elevated the protein expression levels of JNK3, c-Jun and P110 β (*Figure 7*).

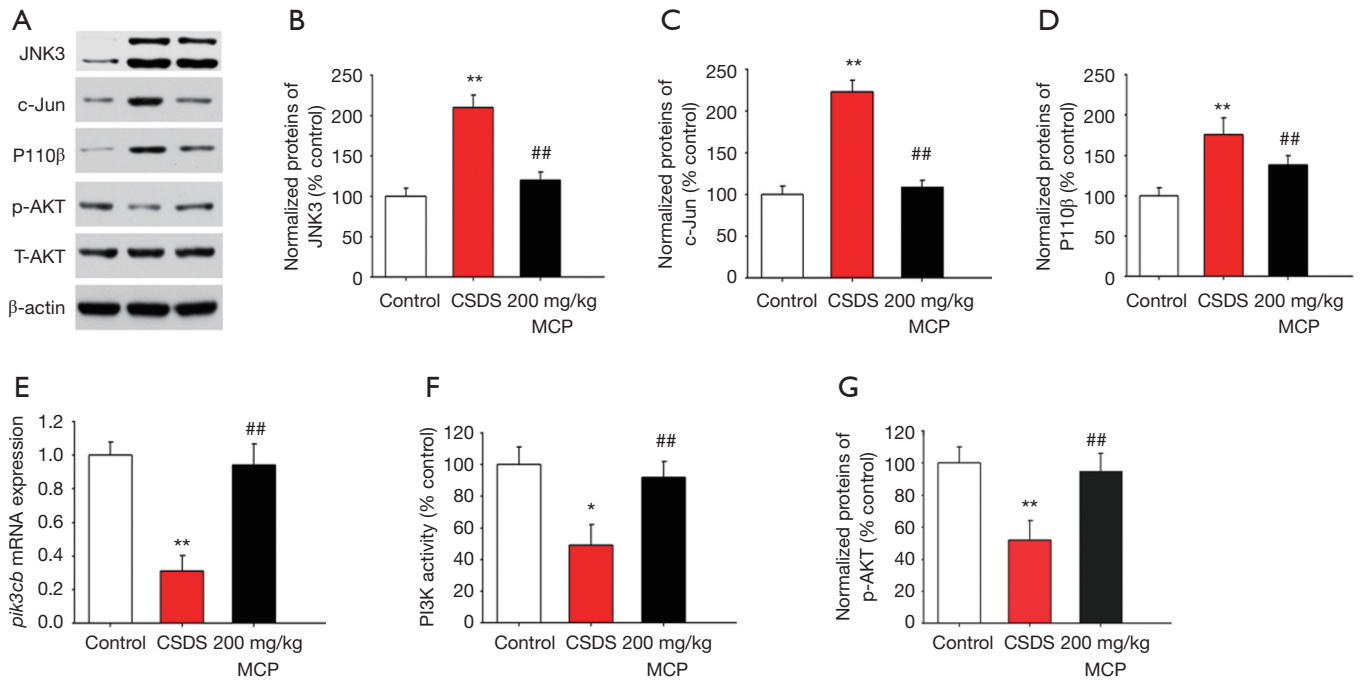

Figure 4 Effect of MCP on expressions of JNK and downstream targets in the hippocampus of CSDS mice. (A) Picture of western blot; (B) expression of JNK3; (C) c-Jun; (D) P110β expression; (E) *pik3cb* mRNA expression; (F) PI3K activity; and (G) p-AKT expression level. The data are expressed as means ± SEM (n=4); *, P<0.05; **, P<0.01 compared to control; ##, P<0.01 compared to CSDS group. MCP, Momordica charantia polysaccharides; CSDS, chronic social defeat stress.

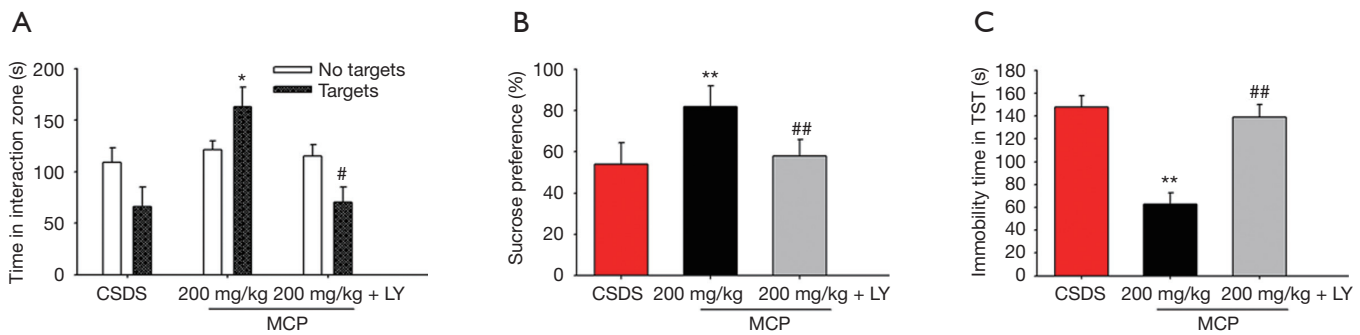

Figure 5 The behaviors of CSDS mice after MCP treatment and the delivery of the PI3K inhibitor LY294002. (A) Social interaction test; (B) sucrose preference test; and (C) tail suspension test. The data are expressed as means ± SEM (n=10); *, P<0.05 and **, P<0.01 compared to CSDS group; #, P<0.05 and ##, P<0.01 compared to 200 mg/kg group. MCP, Momordica charantia polysaccharides; CSDS, chronic social defeat stress.

Discussion

The present study provides behavioral and neurochemical evidence to demonstrate that MCP has neuroprotective effects against depressive-like behaviors. Our results show that depressive-like behaviors induced by CSDS, as evaluated using SIT, SPT and TST, are similar to those of previous findings (31,32). More importantly, MCP significantly protects against these behavioral deficits, and inhibits the protein expression of JNK3 in the hippocampus of CSDS mice. This data suggests that a JNK3/PI3K/

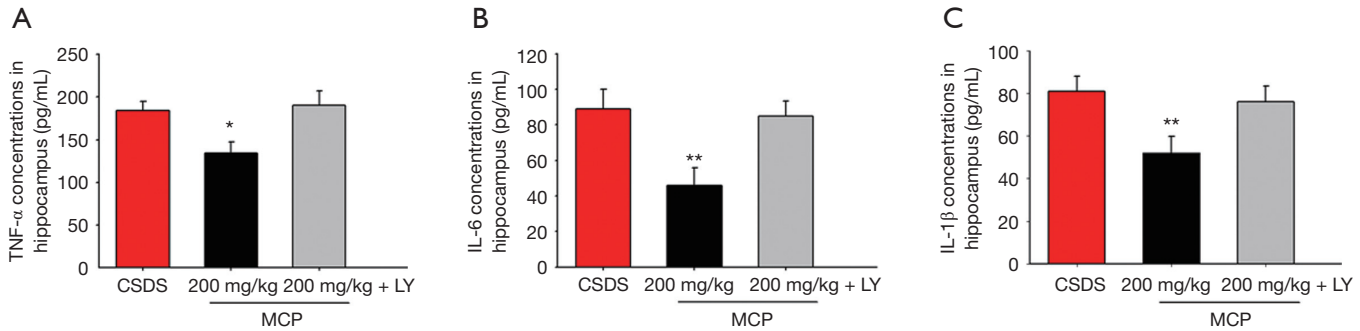

Figure 6 The concentration of pro-inflammatory cytokines in the hippocampus of CSDS mice after MCP treatment and the delivery of the PI3K inhibitor LY294002. (A) TNF-α; (B) IL-6; and (C) IL-β. The data are expressed as means ± SEM (n=10); *, P<0.05 and **, P<0.01 compared to CSDS group. MCP, Momordica charantia polysaccharides; CSDS, chronic social defeat stress.

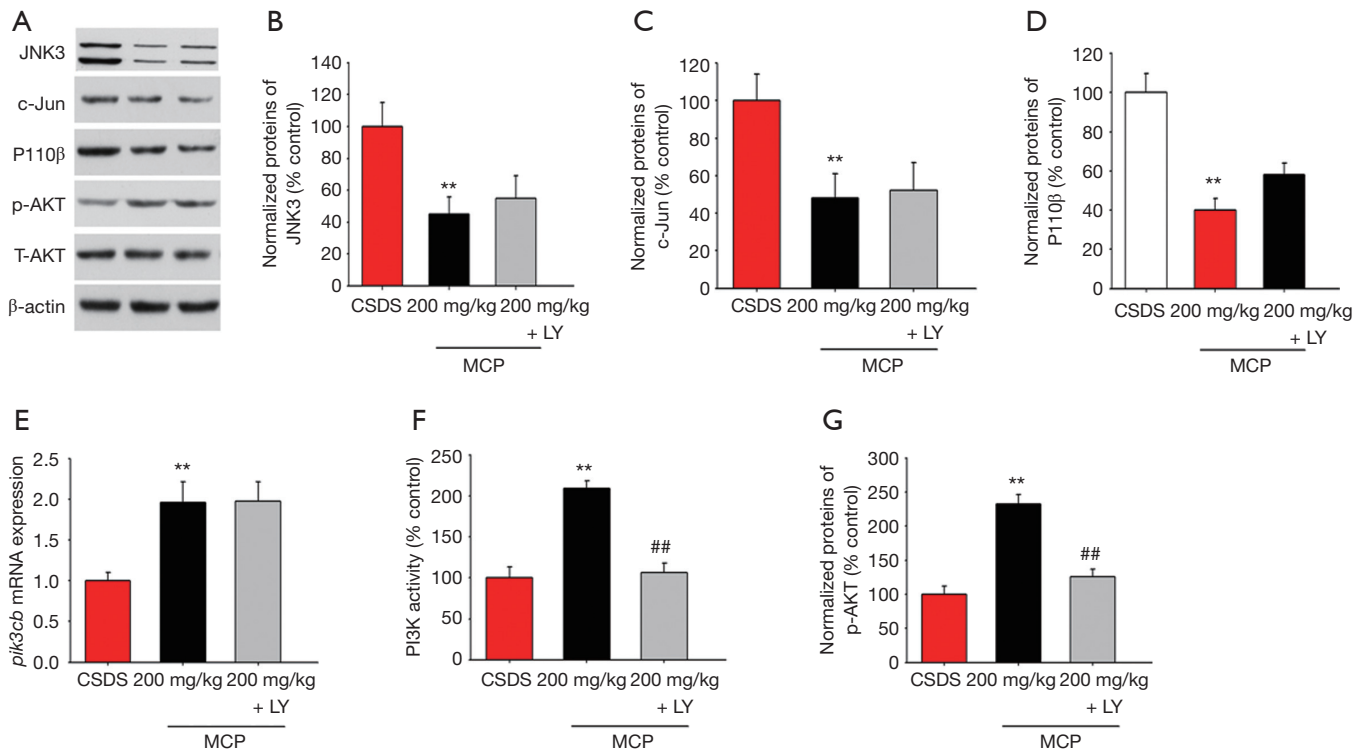

Figure 7 The expressions of JNK and downstream targets in the hippocampus of CSDS mice after MCP treatment and the delivery of the PI3K inhibitor LY294002. (A) Picture of western blot; (B) expression of JNK3; (C) c-Jun; (D) P110β expression; (E) *pik3cb* mRNA expression; (F) PI3K activity; and (G) p-AKT expression level. The data are expressed as means ± SEM (n=4); **, P<0.01 compared to CSDS group; ##, P<0.01 compared to 200 mg/kg group. MCP, Momordica charantia polysaccharides; CSDS, chronic social defeat stress.

AKT cascade might be responsible for the effects of MCP in CSDS mice. MCP exhibits various interesting pharmacological properties such as inhibition of oxidative stress, inflammation and apoptosis (33). Previous studies also show that elevated levels of TNF-α, IL-6 and IL-1β are related to resistance and severity of depressive symptoms (34). In addition, depression is always associated with release of pro-inflammatory factors and an increase in neuronal cell death in the hippocampus (26). The present study demonstrates that TNF-α, IL-6, and IL-1β

are up-regulated in the hippocampus of CSDS mice, and down-regulated after MCP treatment. These results strongly suggest that MCP has anti-depressant and anti-inflammatory effects. Thus, we hypothesize that MCP reduces inflammation and thereby decreases depressive-like behaviors.

JNK isoforms display distinct expression patterns in the hippocampus. JNK3 is observed in hippocampal sub-regions, as well as the dentate gyrus. Studies show that acute stress increases phosphorylation and activity of JNK within hippocampal sub-regions, and JNK inhibitors completely prevent the impairment of conditioned fear. These studies indicate that JNK activity is required for stress-impaired fear conditioning (12). JNK3 may be a crucial factor for stress-induced amnesia and might be important for neuroprotective therapy. A previous study suggests that there is a cross-talk between the JNK and PI3K pathway, specifically involving the JNK3 isoform. The study also shows that a lack of *Jnk3* expression increases *pik3cb* transcript levels, which leads to an increase in PI3K activity (16). In this study, CSDS increased JNK3 expression and reduced *pik3cb* transcript levels. It also inhibited PI3K activity and decreased phosphorylated AKT expression. To the best of our knowledge, this study provides novel evidence linking the JNK3/PI3K/AKT pathway to depressive-like behaviors in CSDS mice, which can be mitigated by MCP intervention.

Brain derived neurotrophic factor (BDNF) has been strongly associated with depression and hippocampal neurogenesis (35). The activation of PI3K up-regulates the expression of VGF and BDNF in the hippocampus (36). Numerous studies have reported that PI3K, the main component of the PI3K/AKT pathway, plays an important role in the production of BDNF (22,37,38). Furthermore, AKT reduces depressive-like and manic-like behaviors by inhibiting GSK3 (39,40). Studies have also demonstrated that the PI3K/AKT/FoxO3a pathway functions as a target for fluoxetine (39). Our results show that LY294002 partly abolishes the antidepressant-like effects of MCP and reduces the protein expression levels of phosphorylated AKT, inhibits the activity of PI3K and mRNA expression of *pik3cb*, and elevates the protein expression levels of JNK3, c-Jun and P110 β. We therefore speculate that the ameliorative effects of MCP on depressive-like behaviors might be partly attributed to the regulation of the JNK3/PI3K/AKT pathway.

In summary, our study provides new insights in to understanding the pathophysiology of depression and the pharmacological effects of MCP. The belief that "natural is better" has led to public interest in herbal medicines, and to the development of antidepressants like ginsenosides and St. John's wort (40,41). Our results shed light on the potential of MCP in preventing depression.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study is in compliance with the National Institute of Health and the Animal Care, Inspection by members in The Medical Animal Care & Welfare Committee of Three Gorges University (No. 2017060q).

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