Polydatin Prevents Neuroinflammation and Relieves Depression via Regulating Sirt1/HMGB1/NF-κB Signaling in Mice

Hetao Bian · Ling Xiao · Liang Liang · Yinping Xie · Huiling Wang · Mark Slevin · Wen-Jun Tu· Gaohua Wang

Abstract

Depression is a prevalent psychiatric disorder with a significant health impact and economic burden worldwide. Unfortunately, the exact pathogenesis of depression is not well understood. Neuroinflammation and microglial activation play an essential role in the pathogenesis of depression. Previous studies have shown that polydatin has anti-inflammatory and antioxidant properties. However, the link between polydatin and depression remains unclear. Therefore, the objective of this study was to investigate the antidepressant effect of polydatin in lipopolysaccharide (LPS)-induced depression in mice and its possible mechanism. Adult male C57BL/6 J mice were used in this study. The polydatin and LPS were injected intraperi-toneally daily for 5 days. In addition, the EX527, an inhibitor of Sirt1, was injected intraperitoneally daily and 1 h before the polydatin injection. The behavior tests were performed to elucidate the depression-like behaviors. The Sirt1/HMGB1/NF-κB pathway expression was detected by western blot, ELISA, and immunofluorescence staining. Polydatin can significantly improve LPS-induced depression-like behavior in mice. Treatment with polydatin increased the expression of the Sirt1 but decreased the expression of the HMGB1, p-NF-κB, IL-1b, and TNF-α in the LPS-induced depression mice. In addition, the EX527 abolished the anti-depressive effects of the polydatin and the levels of Sirt1 protein. These findings suggested that the polydatin reversed the depressive effects through the Sirt1/HMGB1/NF-κB signaling in the LPS-induced depression mice. Therefore, polydatin can be used in the treatment of depression.

Keywords Neuroinflammation · Polydatin · Lipopolysaccharide · sirt1 · Depression

Introduction

Depression is a prevalent psychiatric disorder affecting health substantially and resulting in high treatment costs worldwide (Afridi and Suk 2021). Depression as a psychiatric illness negatively affects the behavior and daily life of the patients (Bouguiyoud et al. 2022; Peritore et al. 2020). Treatment of depression targets balancing neurotransmitters. However, the current treatment methods targeting neurotransmitters are less effective (Empana et al. 2021). Therefore, new effective interventions for the treatment of depression need to be developed, which requires a better understanding of the pathophysiological mechanisms of depression.

Neuroinflammation and microglial activation play an essential role in the pathogenesis of depression (Jia et al. 2021; Yu et al. 2020). Several inflammatory factors, such as tumor necrosis factor α (TNF-α) and interleukin β (IL-1β), modulate neuronal functions contributing to the symptoms of depression (Jiang et al. 2020; Tomaz et al. 2020). Mounting evidence reveals the protective role of neuroinflammatory modulators in the animal models of depression (Song et al. 2020; Tang et al. 2018). In addition, previous studies demonstrate that the microglia sense the depression-related stressors and elicit a neuroinflammatory response that contributes to the development of depression (Giridharan et al. 2019; Guo et al. 2020).

High mobility group box 1 (HMGB1) is a common nuclear protein that modifies the DNA architecture by binding, bending, and looping and is a significant mediator in numerous neuroinflammatory diseases (Rana et al. 2021). Under normal conditions, the HMGB1 is located in the nucleus of cells and regulates transcription and translation (Xie et al. 2021). However, several pathological conditions can promote the transfer of HMGB1 from the cell nucleus into the extracellular region, which induces inflammatory responses (Xu et al. 2020b). Furthermore, once the HMGB1 is released, it binds to the receptor TLR4 and activates TLR4/NF-κB signaling, resulting in an inflammatory cascade (Su et al. 2020).

Silent information regulator 1 (Sirt1) is a nuclear histone deacetylase. The Sirt1 participates in the pathophysiology of depression (Liu et al. 2020; Zhang et al. 2021). Upregulating the Sirt1 inhibited the inflammatory response caused by depression and provided some protection against the sequelae of depression (Arioz et al. 2019). Recent studies have shown that the Sirt1 regulates the HMGB1 transcription through direct deacetylation (Li et al. 2020; Zhang et al. 2020d).

Polydatin is a derivative of resveratrol and acts as a powerful antioxidant (Ma et al. 2016; Park et al. 2019; Yousef et al. 2021). Polydatin also has anti-inflammatory and neuroprotective effects (Shah et al. 2019). In addition,

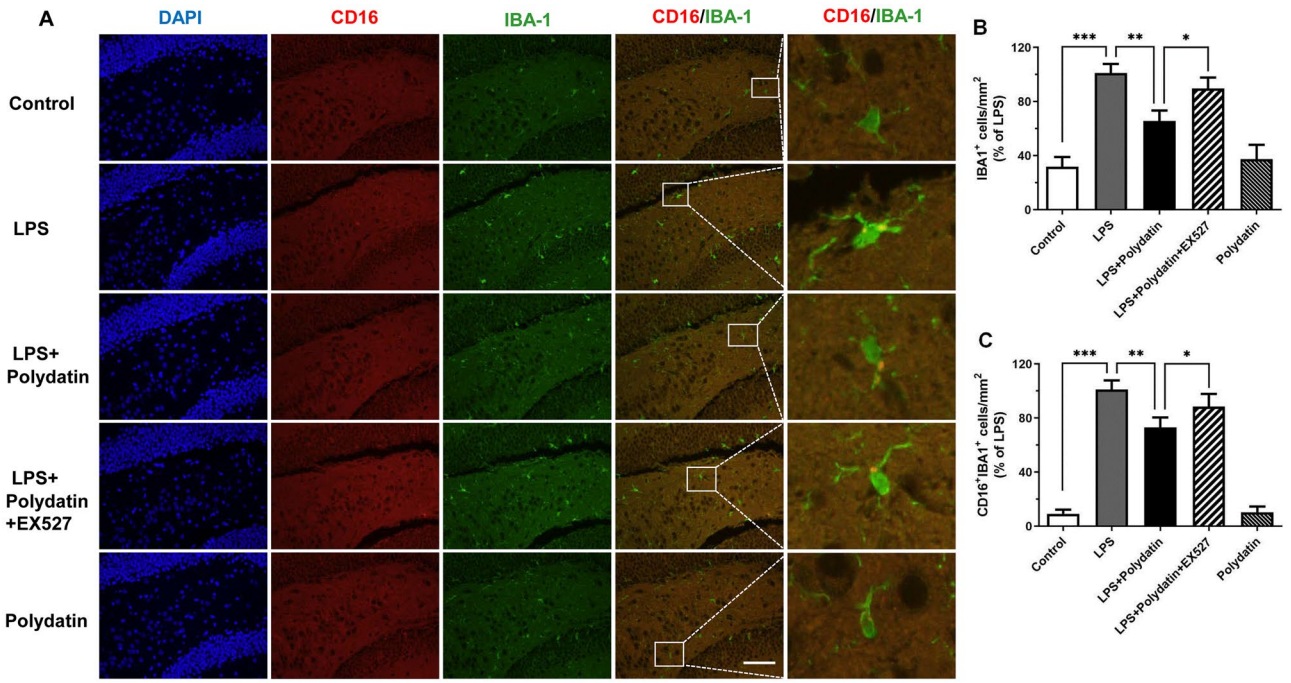

Fig. 1 Blockade of Sirt1 abolished the inhibition of microglia activation effect of Polydatin. **A** Images of immunofluorescence of IBA-1 and CD16 in the mice hippocampus. **B-C** Statistical graphs of IBA-1 (**B**), and IBA-1/CD16 (**C**) signal intensity. Scale bars represent 50 μm. Six micrographs from three mice per group were analyzed. ($^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$)

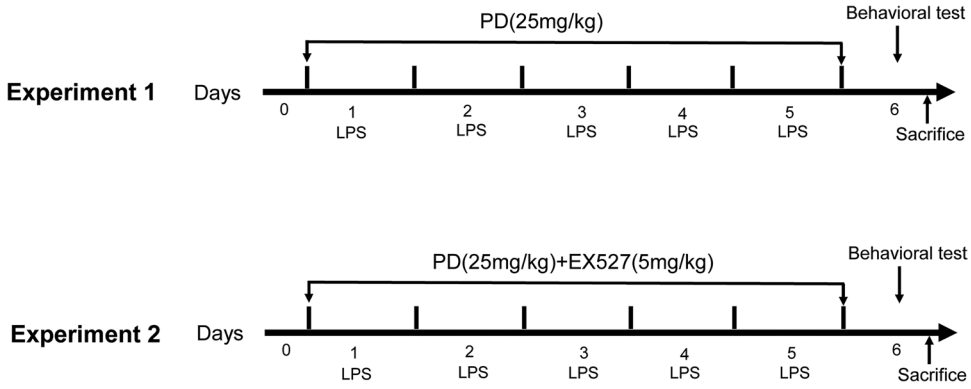

Fig. 2 Experimentaldesign. Experiment 1: Effects of the polydatin on depression-like behaviors inmice. Experiment 2: Study on the mechanism of polydatin improving depressive-behavior in mice

Polydatin is a Sirt1 activator that can reduce the inflammatory response caused by depression by activating the Sirt1 (Sun et al. 2021). However, the effect of polydatin on depression has not yet been studied. Therefore, this study aimed to investigate the antidepressant effects of polydatin and to elucidate the relationship of polydatin with the Sirt1/HMGB1/NF-κB signaling pathway.

Results

Polydatin Ameliorate Depressive Behavior Induced by LPS

Weight determination and behavioral tests including OFT and FST were used to assess the effects of polydatin on LPS-induced depressive behavior in mice.

In Fig. 1A, two-way ANOVA revealed the major role of body weight in the levels of LPS [$F=146.77$; $P<0.001$] and polydatin [$F=0.911$; $P=0.336$], interaction between LPS and polydatin [$F=4.149$; $P=0.055$].

In Fig. 1B, two-way ANOVA revealed the major role of LPS [$F=16.844$; $P<0.001$] and polydatin [$F=3.356$; $P=0.089$], interaction between LPS and polydatin [$F\ (1,20)=5.514$; $P<0.05$]. The multiple analysis showed that polydatin could markedly reduce immobility time in the FST ($P<0.05$).

In Fig. 1C, two-way ANOVA revealed the major role of LPS [$F=18.695$; $P<0.001$] and polydatin [$F=4.078$; $P=0.079$], interaction between LPS and polydatin [$F=9.966$; $P<0.001$]. The multiple analysis showed that polydatin could ameliorate the total distance reduction induced by LPS in the OFT ($P<0.05$). In Fig. 1D, two-way ANOVA revealed the major role of LPS [$F=18.695$; $P<0.001$] and polydatin [$F=4.078$; $P=0.079$], interaction between LPS and polydatin [$F=9.966$; $P<0.001$]. The multiple analysis showed that the polydatin ameliorated the reduction speed induced by LPS in OFT ($P<0.05$). In Fig. 1E, two-way ANOVA revealed the major role of LPS [$F=18.196$; $P<0.001$] and polydatin [$F=1.958$; $P=0.166$], interaction between LPS and polydatin [$F=5.276$; $P<0.05$]. Multiple analysis showed that the polydatin improved the rearing frequencies induced by LPS in the OFT ($P<0.05$).

Polydatin Ameliorated Depressive-Like Behavior Induced by LPS Through Sirt1/HMGB1/NF-κ B Dependent Signaling Pathway

The western blot and ELISA were used to detect the expression of the molecules involved in the Sirt1/HMGB1/NF-κB signaling pathway in response to the antidepressant behavior of polydatin.

The western blot bands of Sirt1/HMGB1/NF-κB signaling pathway were shown in Fig. 2A. As shown in Fig. 2B, two-way ANOVA revealed the major role of LPS [$F=7.008$; $P<0.05$] and polydatin [$F=88.021$; $P<0.001$], interaction between LPS and polydatin [$F=9.690$; $P<0.01$]. The multiple analysis suggested that the polydatin ameliorated the LPS-induced Sirt1 expression ($P<0.001$). In Fig. 2C, two-way ANOVA revealed the major role of LPS [$F=25.949$; $P<0.0001$] and polydatin [$F=3.321$; $P=0.084$], interaction between LPS and polydatin [$F=13.229$; $P<0.01$]. The multiple analysis suggested that the polydatin ameliorated the expression of HMGB1 induced by LPS ($P<0.01$). In Fig. 2D, two-way ANOVA revealed the major role of LPS [$F=57.886$; $P<0.001$] and polydatin [$F=17.911$; $P<0.001$], interaction between LPS and polydatin [$F=31.741$; $P<0.001$]. The multiple analysis suggested that the polydatin ameliorated the expression of p-NF-κB induced by LPS ($P<0.01$).

The western blot band of IL-1β was shown in Fig. 3A. As shown in Fig. 3B, two-way ANOVA revealed the major role of LPS [$F=18.827$; $P<0.001$] and polydatin [$F=3.253$; $P=0.086$], interaction between LPS and polydatin [$F=7.066$; $P<0.05$]. The multiple analysis suggested that the polydatin treatment ameliorated the LPS-induced

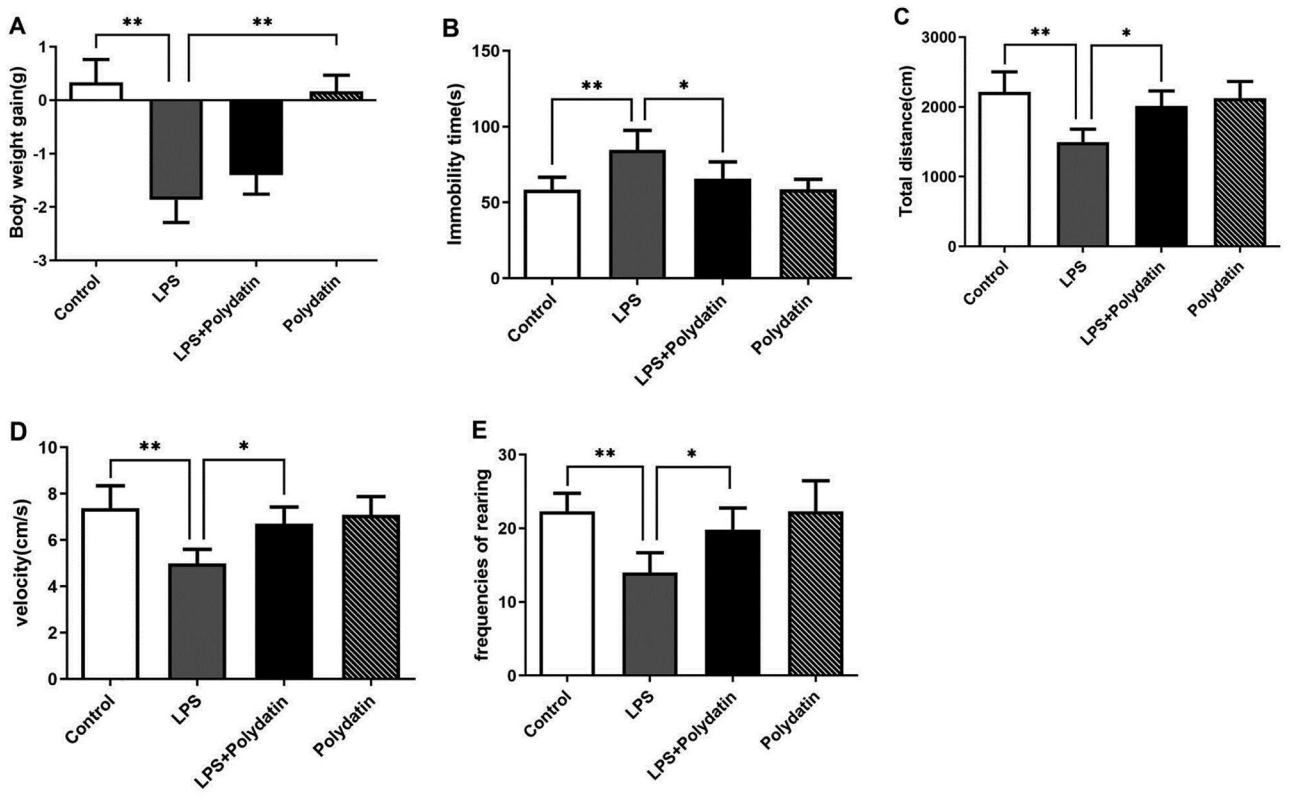

Fig. 3 Effectof the polydatin treatment on depression-like behaviors in mice. **A** Bodyweight changes. **B**–**E** Depressive behaviors were assessed using theforced swimming and open field tests. (*$P < 0.05$, **$P < 0.01$)

IL-1β expression ($P < 0.01$). In Fig. 3C, two-way ANOVA revealed the major role of LPS [$F = 35.920$; $P < 0.001$] and polydatin [$F = 2.392$; $P = 0.138$], interaction between LPS and polydatin [$F = 10.420$; $P < 0.01$]. The multiple analysis suggested that the polydatin ameliorated the expression of TNF-α induced by LPS ($P < 0.05$).

Inhibition of Sirt1 Eliminated the Antidepressant and Anti-inflammatory Effects of Polydatin

The EX527 was administered to investigate whether polydatin alleviates inflammation and improves LPS-induced depression in mice by Sit1.

In Fig. 4A, the mice in the LPS group revealed high body weight loss compared with the mice in the control group ($F = 66.553$, $P < 0.0001$). However, the difference between the polydatin and LPS groups was not significant ($P = 1.0$).

In Fig. 4B, the mice in the polydatin group revealed less immobility time than the LPS group in the FST ($F = 13.386$, $P < 0.001$). However, EX527 reduced the immobility time compared with polydatin group in the FST ($P < 0.05$). In Fig. 4C–E, the total distance, total velocity, and rearing frequencies were reduced in the polydatin group compared with LPS group (total distance $F = 14.065$, $P < 0.0001$; rearing frequencies $F = 15.8161$, $P < 0.001$; velocity $F = 14.065$, $P < 0.001$). EX527 markedly reduced the total distance compared to the polydatin group ($P < 0.01$). At the same time, EX527 reduced the rearing frequencies and total velocity compared with polydatin group (both $P < 0.05$).

In Fig. 5A–D, the western blot result revealed the significant difference between these groups by the one-way ANOVA with respect to the Sirt1 ($F = 14.120$, $P < 0.001$), HMGB1 ($F = 25.019$, $P < 0.0001$), and p-NF-κB ($F = 11.138$, $P < 0.001$). The multiple analysis suggested that polydatin could significantly increase Sirt1 expression in mice compared with the LPS group ($P < 0.01$). Meanwhile, polydatin could significantly decrease HMGB1 ($P < 0.01$) and p-NF-κB ($P < 0.01$) expression in mice compared with LPS group. The inhibition of the Sirt1 by the EX527 eliminated the effect of polydatin, resulting in the decrease of Sirt1 ($P < 0.01$) and the increase of HMGB1 ($P < 0.05$) and p-NF-κB ($P < 0.05$).

In Fig. 6A–B, the western blot data revealed a statistically significant difference among these groups by the one-way ANOVA regarding the IL-1β ($F = 21.001$, $P < 0.0001$). Furthermore, the multiple analysis suggested that polydatin could significantly decrease IL-1β expression in mice compared with the LPS group ($P < 0.01$). The inhibition of the Sirt1 by the EX527 eliminated the effect of polydatin, which led to increased IL-1β ($P < 0.05$).

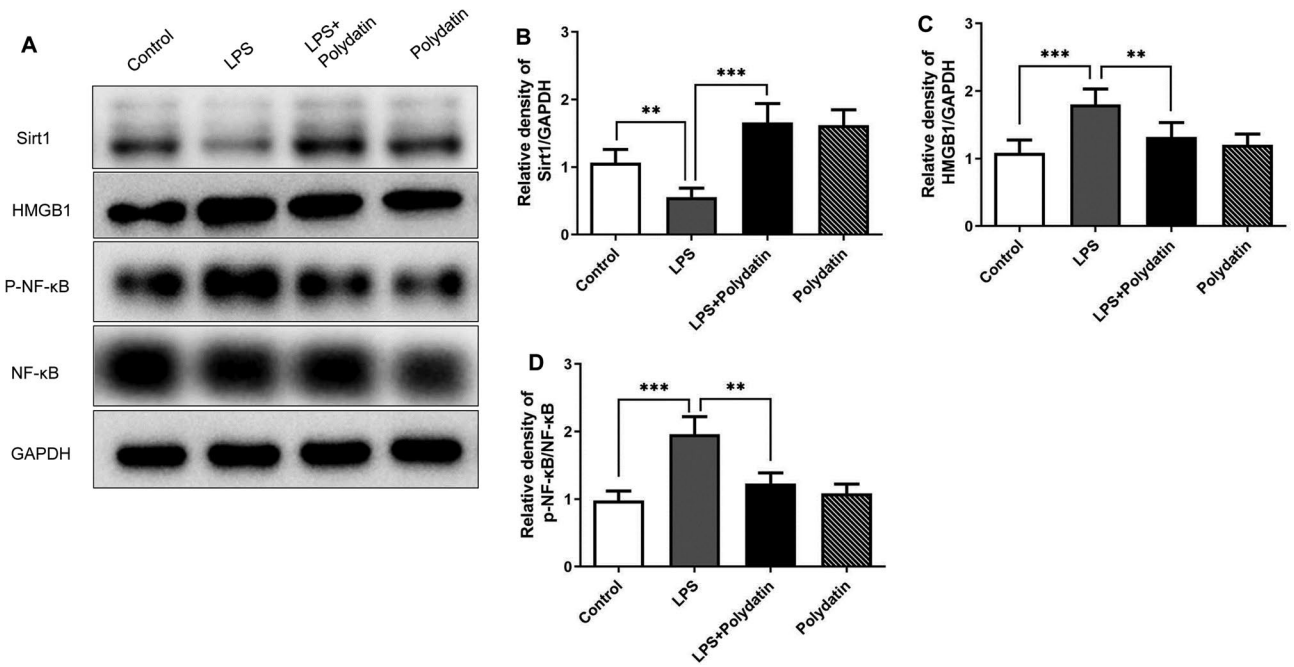

Fig. 4 Effectof polydatin on Sirt1/HMGB1/NF-κB signaling pathway. **A** Western blotbands. Statistical graphs for the protein expression of Sirt1 (**B**), HMGB1(**C**), and p-NF-κB/ NF-κB (**D**). (***P* < 0.01, ****P*< 0.001)

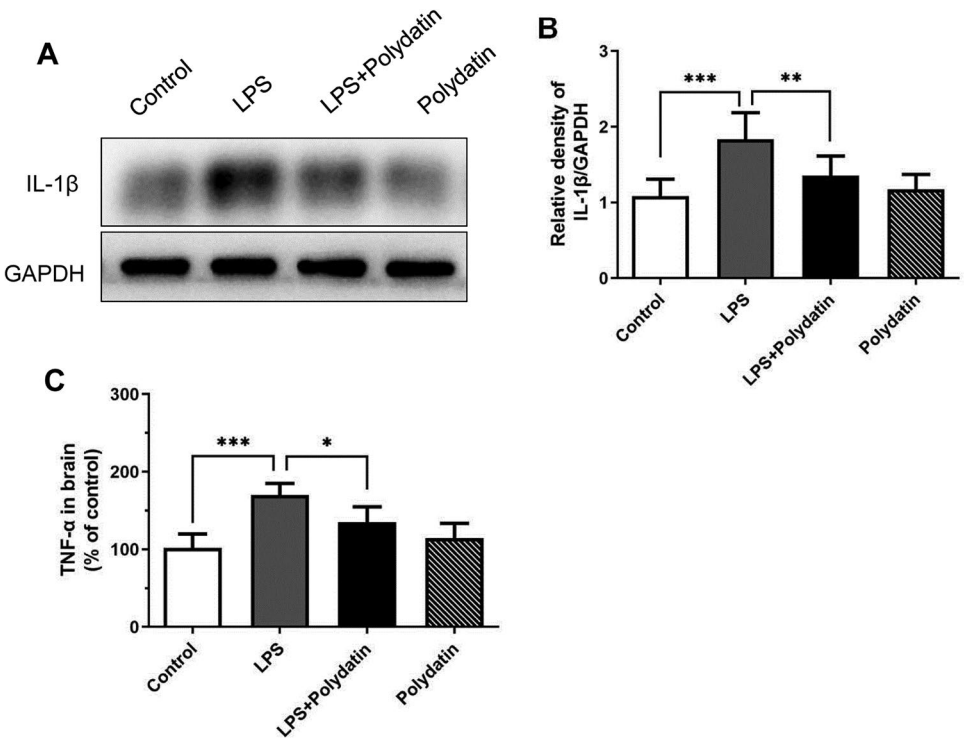

Fig. 5 Effect of polydatinon IL-1b and TNF-α expression. **A** Western blotbands. **B** Statistical graphs for the expression of IL-1b. **C**Statistical graphs for the expression of TNF-α. (**P* < 0.05, ***P*< 0.01, ****P* < 0.001)

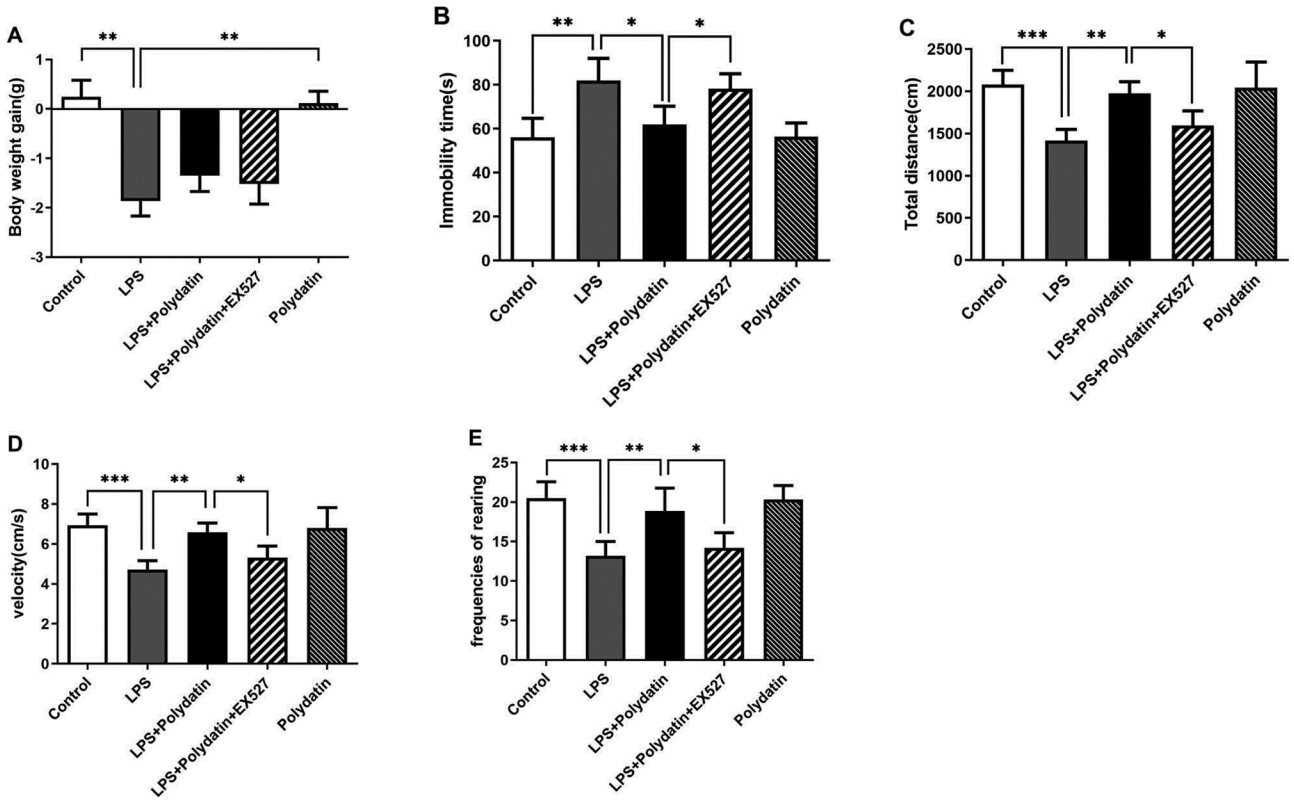

Fig. 6 Blockadeof Sirt1 abolished the anti-depression effect of polydatin. **A** Bodyweight changes. **B**–**E** Depression-like behaviors were assessed byforced swimming test and open field test. (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$)

In Fig. 6C, the ELISA data revealed a statistically significant difference among these groups by the one-way ANOVA regarding the TNF-α ($F = 15.227$, $P < 0.0001$). The multiple analysis suggested that polydatin could significantly decrease TNF-α expression in mice compared with the LPS group ($P < 0.0001$). At the same time, the inhibition of the Sirt1 by the EX527 eliminated the effect of polydatin, which led to increased TNF-α ($P < 0.05$).

Blockade of Sirt1 Abolished the Inhibition of Microglia Activation Effect by the Polydatin

The expression of IBA-1 and CD16 was detected to determine microglia activation. In Fig. 7A and B, the mice exposed to the polydatin showed less microglial activation with the decrease of IBA-1 protein abundance compared with the LPS group ($F = 84.631$, $P < 0.01$). At the same time, the inhibition of the Sirt1 by the EX527 decreased the microglia activation ($P < 0.05$).

As shown in Fig. 7A and C, the mice exposed to the polydatin showed less microglial activation with decreased IBA-1 and CD16 protein abundance than the LPS group ($F = 279.976$, $P < 0.01$). The inhibition of the Sirt1 by the EX527 decreased the microglia activation ($P < 0.05$).

Discussion

The current study suggested that polydatin can improve LPS-induced depression-like behavior in mice and was associated with upregulation of Sirt1; downregulation of HMGB1, P-NF-κB, IL-1β, and TNF-α; and the inhibition of microglia activation. The inhibition of the Sirt1 by the EX527 eliminated the anti-depressant effect of the polydatin, which was related to the low expression of the Sirt1; upregulation of the HMGB1, p-NF-κB, IL-1β, and TNF-α; and the activation of microglia. Altogether, these results indicated that the polydatin protected against the LPS-induced depression-like behaviors and was associated with inhibiting neuroinflammation and microglia activation through the Sirt1/HMGB1/NF-κB signaling pathway in mice. Thus, this current study may reveal an effective potential candidate drug to prevent depression.

Polydatin is a kind of traditional Chinese medicine with extensive pharmacological activities, with anti-inflammatory and antioxidant effects (Wu et al. 2020). Moreover, some studies have demonstrated that the polydatin exhibited neuroprotective effects against ischemic stroke and Parkinson's disease (Gao et al. 2016; Huang et al. 2018). However, no study has been published on the use of polydatin for depression. As far as we know, this was the first study to evaluate

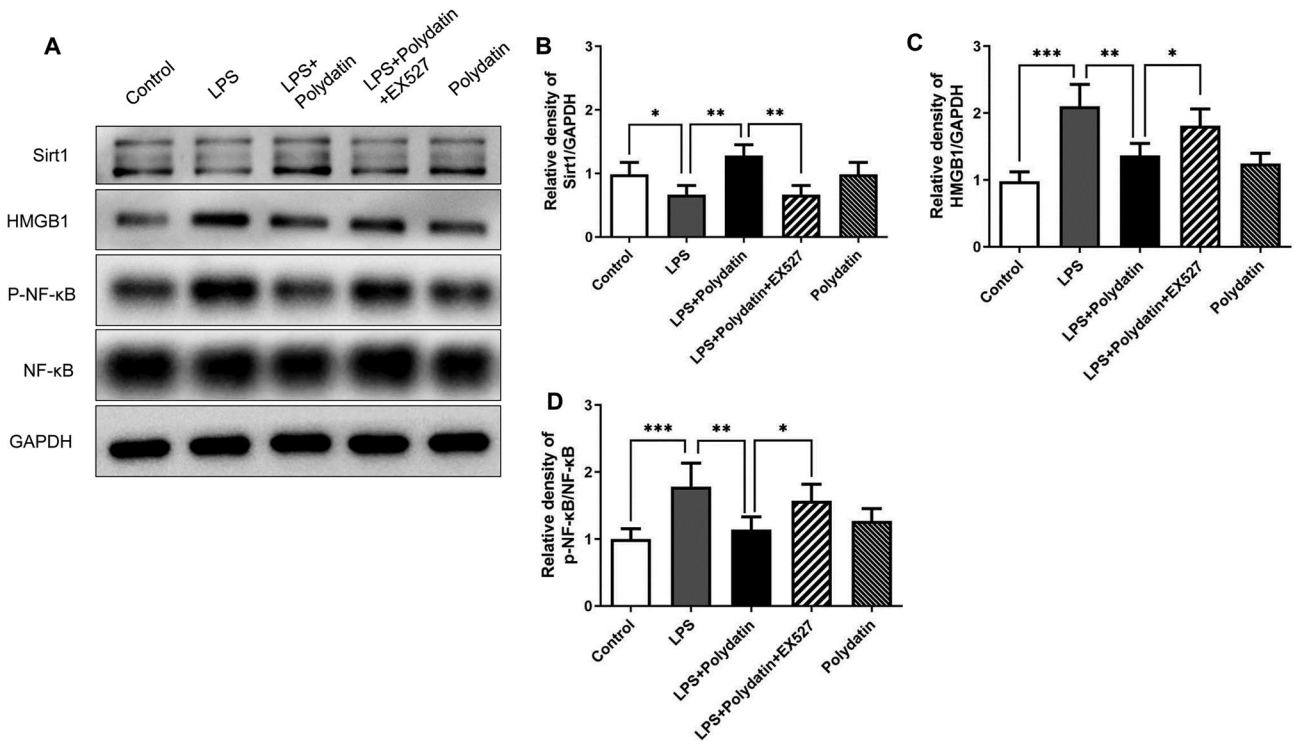

Fig. 7 Blockadeof Sirt1 abolished the effect of polydatin on Sirt1/HMGB1/NF-κB pathway. **A**Western blot bands. Statistical graphs for the expression of Sirt1 (**B**),HMGB1 (**C**), and p-NF-κB/NF-κB (**D**). (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$)

the antidepressant effects of polydatin. The present study found that polydatin improved the depression-like behavior induced by the LPS in mice. These results showed that polydatin could be an effective treatment for depression.

Depression is a common mental disorder worldwide, with a vast socioeconomic impact (Kohler-Forsberg et al. 2020). Increasing evidence suggests that the activation of immune inflammation leads to depression (Hayley et al. 2021; Sulakhiya et al. 2014). The inflammatory challenge induced by the LPS exhibits depressive-like behavior in animal models (He et al. 2020; Tang et al. 2020). Previous studies have shown that anti-inflammatory activity can improve depressive-like behaviors (Ali et al. 2020a). The NF-κB is a protein complex that is known to be associated with the pathogenesis of inflammatory diseases such as stroke and depression (Liu et al. 2021; Yang et al. 2019). Furthermore, the NF-κB activation in the hippocampus regulated the inflammatory response and microglial activation (Zhang et al. 2020c). Under normal physiological conditions, the NF-κB binds to IκB and remains inactive in the cytoplasm (Moser et al. 2021; Shih et al. 2015). Once activated, the IκB is phosphorylated and degraded, leading to the NF-κB(p65) phosphorylation and transcriptional regulation of inflammatory factors such as IL-1β and TNF-α (Bampi et al. 2020). The present study identified that the expression of the p-NF-κB, IL-1β, and TNF-α was increased after LPS treatment. After the administration of polydatin, the level of the p-NF-κB, IL-1β, and TNF-α decreased markedly. Therefore, we hypothesized that polydatin might improve the depressive behaviors induced by the LPS in mice by regulating the NF-κB mediated inflammation.

The HMGB1 is a critical inflammatory mediator, which promotes inflammation when released by immune cells (Paudel et al. 2020; Xue et al. 2021). The biological activity of the HMGB1 depends on its location. Once released from the nucleus into the extracellular space, the HMGB1 binds to the receptor TLR4 and activates the TLR4/NF-κB pathway, ultimately leading to inflammation (Qiu et al. 2021; Xu et al. 2020a). In recent days, the HMGB1 has been studied in several neurological diseases, including depression (Guo et al. 2019; Wang et al. 2018). HMGB1 can mediate depressive behavior induced by chronic stress response (Liu et al. 2019). It was reported that the minocycline exerts an anti-depressive action by inhibiting the HMGB1 pathway (Wang et al. 2020a). Our study found that the HMGB1 levels were elevated after the LPS treatment, suggesting that the HMGB1 may have mediated the onset of depression. We also found that the expression of HMGB1 was decreased after the polydatin treatment. These findings indicated that the HMGB1 might have been associated with depression, while polydatin could have been improved depression.

The Sirt1 is a protein deacetylase that regulates various cell functions. It has been demonstrated that the Sirt1 plays an anti-inflammatory role by interfering with the HMGB1 signal (Chibaatar et al. 2021). Activation of the Sirt1 was used to treat various inflammation-related diseases such as depression (Kim et al. 2016; Lu et al. 2018). It was reported that melatonin exerts an anti-depressive action by targeting the Sirt1 signaling (Ali et al. 2020a). In our study, we found that the polydatin treatment increased the expression of the Sirt1, which was abrogated when the EX527 downregulated Sirt1. At the same time, the expression of the HMGB1 decreased after the treatment with polydatin, and the EX527 abolished the decrease of HMGB1. These results indicated that the polydatin improves the depressive-like behavior induced by the LPS in mice, mainly through Sirt1/HMGB1/NF-κB signaling pathway.

Microglia are immune cells in the brain and play an important neuroprotective role under normal physiological conditions (Perez-Rodriguez et al. 2021; Ye et al. 2020). It has been reported that the microglia involve in the formation and development of depression (Bassett et al. 2021; Zhang et al. 2020b). Pathological activation of the microglia aggravates the neuroinflammation by releasing several inflammatory factors, including IL-6, IL-1β, and TNF-α (Piovan et al. 2021). Neuroinflammation is a crucial driver of the pathogenesis of depression and is mainly regulated by the microglia (Piovan et al. 2021). The present study revealed that microglia activation was significantly enhanced when the LPS treatment induced depression-like behavior in mice. After the polydatin treatment, we found that the activation of microglia was reduced, which was abrogated when the EX527 downregulated the Sirt1.

There are several limitations to the present study. First, we only targeted the Sirt1/HMGB1/NF-κB pathway, and the probability of the involvement of other pathways needs further investigation. Second, our study only focused on the LPS-induced depression model, and the antidepressant effect of polydatin on other depression models needs to be studied.

Conclusions

This study aimed to explore the anti-depressant effects of polydatin in depressed mice, and to examine the contribution of the Sirt1/HMGB1 signaling pathway and microglia activation in this process. In summary, the findings of this study suggested that the polydatin had an antidepressant effect in the LPS-induced mice by regulating the Sirt1/HMGB1/NF-κB mediated inflammatory response and microglial activation. This study has provided theoretical knowledge for the treatment of depression using polydatin.

Methods and Materials

Animals

Adult male C57BL/6 J mice (weight, 20–25 g) were purchased from the Beijing Vital River Laboratory Animal Technology (Beijing, China) and raised at room temperature (17–23 °C) in a 12-h day-night cycle. All experimental procedures were approved by the Institutional Animals Care Committee of Renmin Hospital of Wuhan University (IACUC Issue No. WDRM20191101) and carried out according to its guidelines.

Experimental Design

This study is divided into two experimental parts, as shown in Fig. 8.

Experiment 1: There were four groups ($n=6$ each group): control, LPS, LPS + polydatin, and polydatin. Bodyweight, open field test (OFT), and forced swim test (FST) were tested to evaluate the antidepressant effects of polydatin. The protein expression of the Sirt1, HMGB1, p-NF-κB, and IL-1β was detected by the western blot. In addition, the level of TNF-α was detected by ELISA.

Experiment 2: There were five groups ($n=9$ each group): control, LPS, LPS + polydatin, LPS + polydatin + EX527, and polydatin. Bodyweight, OFT, and FST were measured to evaluate the antidepressant effects of polydatin. The expression of Sirt1, HMGB1, p-NF-κB, and IL-1β was detected by the western blot. The content of the TNF-α was measured by ELISA. The expression of IBA-1 and CD16 was detected by immunofluorescence staining.

Drug Treatment

LPS was dissolved by phosphate-buffered saline (PBS) and administered intraperitoneally (i.p.) at the dosage of 1 mg/kg every day for five injections as described previously (Ali et al. 2020b). The polydatin (MedChemExpress; 98.95% purity) was diluted in DMSO, PEG300, and saline and administered intraperitoneally (i.p.) at the dosage of 25 mg/kg every day for five injections (Guan et al. 2020). The Sirt1 antagonist EX527 (MedChemExpress; 99.87% purity) was diluted in DMSO, PEG300, and saline and administered intraperitoneally (i.p.) at the dosage of 5 mg/kg every day for a total of five injections (Li et al. 2021).

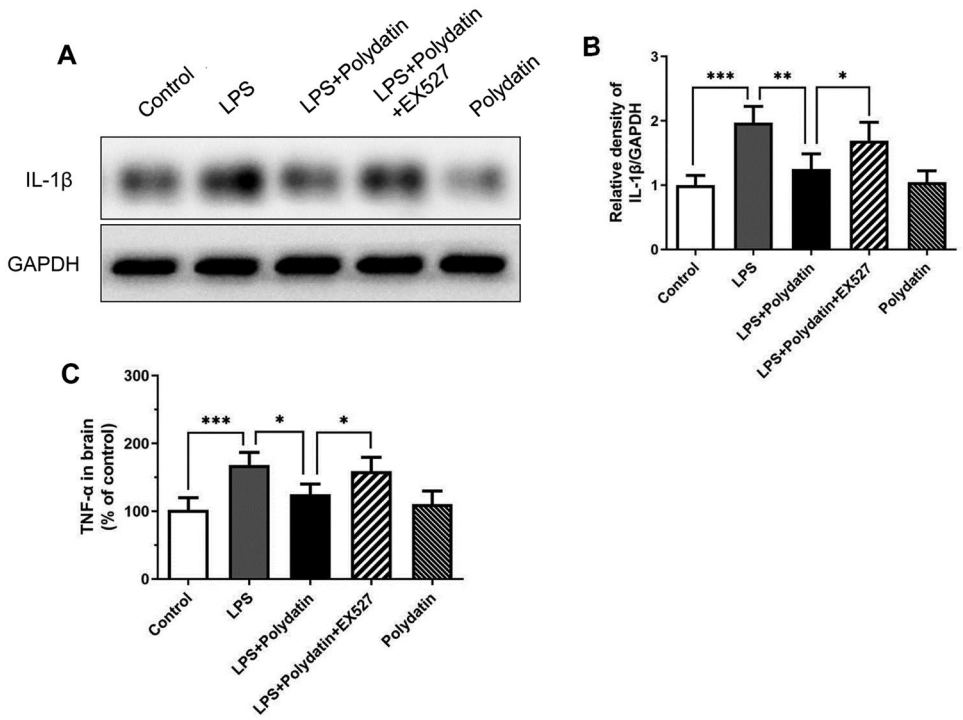

Fig. 8 Blockade of Sirt1 abolished the effect ofpolydatin on IL-1b and TNF-α expression. **A** Western blot bands. **B**Statistical graphs of the expression of IL-1b. **C** Statistical graphs ofexpression of TNF-α. (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$)

FST

The FST was performed according to a previous study (Zhou et al. 2020). First, the mice were trained in a glass cylinder (48 cm × 20 cm) for 15 min. The next day, the mice were placed in the glass cylinder for 6 min, and the immobility time in the last 4 min was recorded.

OFT

The OFT was performed according to a previous study (Zhou et al. 2020). Before the test, the mice were placed in the testing room for more than 30 min to get used to their new environment. Then, the mice were placed in a device made up of 50 cm × 50 cm black squares. The evaluation of each mouse was recorded for 5 min, and the movements were recorded using the video tracking system (Ethovision XT 11.5). Finally, the video tracking system was used to analyze the total distance, speed, and frequency of rearing.

Western Blot

The western blot was performed according to the methods in a previous study (Zhang et al. 2020a). The protein concentration of the hippocampus was detected by the BCA Protein Assay Kit (P0012S; Beyotime, China). The proteins were separated by SDS-PAGE and transferred to polyvinylidene fluoride (PVDF) membrane. The membranes were incubated with the following primary antibodies: Sirt1 (catalog no. ab189494; dilution, 1:1000; Abcam), HMGB1 (catalog no. ab79823; dilution, 1:1000; Abcam), NF-κB (catalog no. 8242S; dilution, 1:1000; CST), p-NF-κB (catalog no. 3033S; dilution, 1:1000; CST), and IL-1β (catalog no. ab9722; dilution, 1:1000; Abcam). The proteins were bound with their respective antibodies. The membranes were washed with the TBST three times and incubated with secondary antibody (catalog no. ab205718; dilution, 1:2000; Abcam), for 1 h. At last, the bands were viewed by ChemiDoc XRS System (Bio-Rad, Hercules, CA, USA), and GAPDH (catalog no. GB11002; dilution, 1:1000; Service, Wuhan, Hubei, China) was used as an internal reference.

ELISA

The brain tissue homogenates lysed in RIPA buffer were used for the ELISA. The levels of TNF-α were detected by following the manufacturer's instructions (Elabscience Biotechnology, Wuhan, Hubei, China).

Immunofluorescence

The previous study performed immunofluorescence staining (Wang et al. 2020b). The slides were blocked in 2% BSA for 1 h. After blocking, the slides were incubated with the antibodies anti-IBA-1 (catalog no. 01919741; dilution,

1:1000; Wako) and CD16 (catalog no. ab25235; dilution, 1:1000; Abcam) at 4 °C overnight. The secondary antibody was incubated the next day to tag the primary antibody on the slide for 1 h in the dark at room temperature. The DAPI was used as the nuclear counterstain.

Statistical Analysis

The data are expressed as mean ± standard error of the mean (SEM). Using GraphPad Prism 8.0 (CA, USA), analysis and mapping were performed. Statistical comparisons were made using one-way or two-way analysis of variance (ANOVA). The P value of < 0.05 considered statistical significance.

Abbreviations TNF-α: Tumor necrosis factor α; IL-1β: Interleukin β; HMGB1: High mobility group box 1; Sirt1: Silent information regulator 1; OFT: Open field test; FST: Forced swim test; PBS: Phosphate-buffered saline; PVDF: Polyvinylidene fluoride

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Author Contribution Drs. WG, TW, and SM contributed equally to this work. They had full access to all the data in the study and took responsibility for the integrity of the data and the data analysis accuracy. Study concept and design: all authors; acquisition of data: BH, XL, LL; analysis and interpretation of data: all authors; drafting of the manuscript: all authors; critical revision of the manuscript for important intellectual content: WG, TW, and SM; statistical analysis: BH; administrative, technical, or material support: all authors; obtained funding: TW; study supervision: WG.

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Availability of Data and Material Please contact the corresponding author (Pro. Wang) for the data request.

Declarations

Consent for Publication Not applicable.

Conflict of Interest/Competing Interest The authors declare no competing interests.

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