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*Original Research Article*

# Study on the Mechanism of Berberine Based on PI3K/mTOR/Autophagy Pathway to Ameliorate Sepsis-associated Encephalopathy Injury

Pharmacognosy Magazine
22(3) 1181–1187, 2026
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DOI: 10.1177/09731296251384399
journals.sagepub.com/home/phm
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## Abstract

**Background:** Sepsis-associated encephalopathy (SAE) is a major cause of high mortality, and no specific therapeutic drugs are currently available. Berberine has been well-documented for its neuroprotective effects, but its mechanism of action remains unclear.

**Objectives:** Use of network pharmacology to study the mechanism of action of berberine (BER) in the treatment of sepsis-associated encephalopathy (SAE).

**Materials and Methods:** Application of network pharmacology to predict the signalling pathway of BER in the treatment of SAE. The mouse model of SAE was constructed, and determination of tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6) and interleukin-10 (IL-10) was done by enzyme-linked immunosorbent assay (ELISA). The effects of BER on neuronal damage in SAE mice were examined by haematoxylin-eosin (HE) staining and Nissl staining. Transmission electron microscopy was used to observe neuronal autophagy formation, and Western blot analysis was employed to explore the mechanism of action.

**Results:** Based on Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses, BER is most likely to treat SAE via the phosphatidylinositol-3 kinase (PI3K)-Akt pathway. TNF-α, IL-1β, IL-6 and IL-10 levels were significantly lower in the BER group than in the SAE group, and the opposite trend was shown in the 3MA group. HE staining and Nissl staining BER were found to significantly reduce SAE injury; terminal deoxynucleotidyl transferase dUTP nick end labelling (TUNEL) and transmission electron microscopy visualised under the microscope that the injured cells were shrunken and apoptosis occurred. Western blotting experiments revealed that PI3K, mammalian target of rapamycin (mTOR), matrix metalloprotein-9 (MMP-9) and p62 were reduced in the BER group as compared to the SAE group; Beclin1 and light chain 3 (LC3) were elevated; the opposite trend was shown in the 3MA group.

**Conclusion:** This study predicted the mechanism of action of BER acting on the PI3K/mTOR signalling pathway for the treatment of SAE and linked more potential therapeutic targets.

## Keywords

Network pharmacology, PI3K/mTOR, autophagy, sepsis-associated encephalopathy, berberine

**Received** 15 May 2025; **revised** 04 July 2025; **accepted** 12 September 2025

## Introduction

Network pharmacology is a holistic approach that uses systems biology and biological network analysis to understand the interactions between drugs and organisms. It emphasises the multi-pathway regulation of signalling pathways to improve the therapeutic effect of drugs and reduce toxic side effects (Zhang et al., 2023). Applying network pharmacology technology and methodology to study the mechanism of action of berberine (BER) by identifying the key nodes and functional modules in the network seems to be the perfect approach.

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Cellular autophagy is a conserved mode of self-degradation in cells, involving the reuse of damaged organelles and macromolecules through lysosomal degradation. The basal level of autophagy is necessary for maintaining cellular homeostasis (Glick et al., 2010). Autophagy is divided into three types according to the way molecules are bound: macroautophagy, microautophagy and chaperone-mediated autophagy (Debnath et al., 2023). Of these, macroautophagy has been the most studied (Sinha, 2023). It has been found that the regulation of autophagy involves multiple signalling pathways, with the adenosine monophosphate-activated protein kinases (AMPK) and rapamycin (mTOR) pathways being central to this regulation (Zhang et al., 2019). AMPK promotes autophagy, whereas mTOR inhibits autophagy (Li et al., 2021; Wang et al., 2023). Free Beclin1 is known to form a phosphatidylinositol-3 kinase (PI3K) complex with various proteins. This complex regulates the localisation of different autophagy-associated ATG proteins in autophagy precursor structures via the PI3K/Akt/mTOR pathway. This process affects autophagy (Sher et al., 2020).

The complexity of the pathophysiological mechanisms of sepsis-associated encephalopathy (SAE) and the diversity and non-specificity of its clinical manifestations make researching this disease difficult. However, the high mortality rate in intensive care units (ICUs) and the lack of specific drugs indicate the necessity and urgency of researching this disease (Tauber et al., 2021). BER is a traditional Chinese medicine preparation with a variety of biological activities. There is a large body of research evidence supporting its effectiveness in treating inflammation, cerebral ischaemia and apoptosis in various encephalopathic manifestations. This suggests that BER may alleviate brain damage caused by SAE (Wang et al., 2017). As a clinically mature preparation, BER can be quickly applied in clinical practice by adding indications, which is extremely valuable for this study. The study has a high degree of feasibility due to the application of network pharmacology focusing on the main signalling pathways, the use of mature molecular biology and the bold assumptions of scientific evidence. There are also prospects for both scientific and economic benefits.

## Materials and Methods

### *Experimental Reagents and Instruments*

BER (YUANYE, CAS: B21379); haematoxylin-eosin (HE) stain reagent kit (Solarbio, CAS: G1120); Nissl stain (Biyuntian, CAS: C0117); terminal deoxynucleotidyl transferase dUTP nick end labelling (TUNEL) apoptosis reagent (Biyuntian, CAS: C1086); tumour necrosis factor-α (TNF-α) enzyme-linked immunosorbent assay (ELISA) kit (Biyuntian, CAS: PT512); interleukin-1β (IL-1β) ELISA kit (Biyuntian, CAS: PI301); interleukin-6 (IL-6) ELISA kit (Biyuntian, CAS: PI326); interleukin-10 (IL-10) ELISA kit (Biyuntian, CAS: PI522); PI3K antibody (Abcam, CAS: ab302958); mTOR antibody (Abcam, CAS: ab134903); light chain 3 (LC3) antibody (Abcam, CAS: ab63817); P62 antibody (Abcam, CAS: ab109012); Beclin1 antibody (Abcam, CAS: ab114071); matrix metalloprotein-9 (MMP-9) antibody (Abcam, CAS: ab76003) and β-actin antibody (Abcam, CAS: ab179467).

### *Prediction of Target Genes and Signalling Pathways by Applying Network Pharmacology*

The corresponding 267 target genes were queried through the PubChem 2024 and SwissTargetPrediction databases, and 2,521 target genes for SAE were queried through the DisGENET database. The target genes of BER and the target genes of SAE were mapped, and 20 common genes were obtained by mapping. The interacting proteins were queried through the interaction database STRING, and the protein interaction network was constructed. The DAVID analysis tool was used to analyse the Gene Ontology (GO) molecular functions and biological processes of the interacting genes. Pathway enrichment analysis of common target genes was performed using Kyoto Encyclopedia of Genes and Genomes (KEGG) database.

### *Sources and Groups of Experimental Animals*

Clean-grade healthy adult male c57BL/6 mice were obtained from the Experimental Animal Centre of Xinjiang Medical University, weighing 20–30 g. The animals were housed in an indoor environment at 21°C and 75% relative humidity. The experimental mice were randomly divided into 5 groups, 10 mice in each group, as follows: Group (1) Con: normal rearing; Group (2) SAE: intraperitoneal injection of saline equal to the amount of the drug and Groups (3–5) BER-L, BER-M and BER-H. According to the clinical dose of BER converted to the dose of mice, BER was given to the model mice by intraperitoneal injection, respectively (150, 200 and 250 mg/kg/d), and after 1 day of administration, the material was taken. 6.3MA: In total, 15 successfully modelled experimental mice were first given an intraperitoneal injection of BER (250 mg/kg/d), followed by 3MA (10 mg/kg/d) for 1 day, after which samples were taken.

### *HE Staining*

Sections were placed in 4% paraformaldehyde fixative for 48 h, rinsed under running water for 8 h and then placed in 75% ethanol for overnight dehydration, followed by gradient dehydration, transparency and embedding in dipping wax on the next day. The embedded paraffin blocks were cut into 5 μm sections using a slicer. Haematoxylin staining time was 5 min, eosin staining time was 5 s, followed by dehydration, transparency and neutral gum sealing.

### *Nissl Staining*

Paraformaldehyde fixed sections, sections were dipped into the toluidine blue stain, the staining vat was placed in a thermostat under 60°C invasion of staining for 30 min, 95%

ethanol rapid differentiation, the sections were placed in anhydrous ethanol for 1 min, anhydrous ethanol for 5 min, xylene I for 5 min, xylene II to dehydration and transparency for 5 min, then taken out from xylene and dried slightly and sealed with neutral gum.

### *TUNEL Staining*

Sections were fixed using 4% paraformaldehyde for 30 min. Samples were treated with 0.1% sodium dodecyl-sulphate (SDS) for 5 min at room temperature. After pre-treatment, samples were incubated with the TUNEL reaction mix. The TdT enzyme and fluorescently labelled dUTP were added to the samples in the proportions recommended by the kit. At 37°C, incubated for 1 h to allow TdTase to recognise and bind to the 3'-OH end of the DNA and added fluorescently labelled dUTP. Washed with phosphate-buffered saline (PBS), dried away from light and sealed the samples.

### *Determination of TNF-α, IL-1β, IL-6 and IL-10 by ELISA*

Frozen brain tissue was homogenised and centrifuged at $1 \times 10^4$ rpm for 5 min in order to collect the supernatant for the determination of TNF-α, IL-1β, IL-6 and IL-10 according to the instructions in the kit.

### *Observation of Autophagosome Formation by Transmission Electron Microscopy*

About 1 × 1 × 1 mm tissues were taken from the mouse cerebral cortex, washed with PBS, fixed in 2.5% glutaraldehyde solution for 2 h, washed with PBS to remove the surface glutaraldehyde and then post-fixed in 1% osmium tetroxide. The tissue was dehydrated with gradient ethanol and acetone, then embedded, sectioned with an ultrathin microtome and double-stained with 3% uranyl acetate and lead citrate, and the structure of neuronal cells was observed under a transmission electron microscope and photographed. Set acceleration voltage (15 kV) and magnification factor (10,000×).

### *Western Blotting*

Approximately 20 mg of brain tissue from the same part of each group was taken, 400 μL of protein lysate was added, homogenised on ice, lysed for 15 min and total protein was extracted. In total, 100 μg of protein samples from each group were subjected to SDS-polyacrylamide gel electrophoresis (PAGE), and membrane transfer for 120 min after protein concentration was determined by bicinchoninic acid (BCA). Approximately, 5% bovine serum albumin (BSA) was incubated on a shaking table at room temperature for 2 h and then incubated with the appropriate ratio of PI3K, mTOR, LC3II, p62, Beclin1, MMP-9 and β-actin antibodies overnight at 4°C. PI3K (1:1,000), mTOR (1:1,000), LC3II (1:1,000), p62 (1:1,000), Beclin1 (1:1,000), MMP-9 (1:1,000) and β-actin (1:2,000) antibodies were incubated overnight at 4°C. The membrane was washed with TBST and then incubated with 1:3,000 diluted goat anti-rabbit IgG at room temperature for 2 h. After the membrane was washed again, electrochemiluminescence was used to develop the exposure, photographs were taken and protein bands were analysed using BIO-RAD software, and β-actin was used as an internal control.

### *Statistical Processing*

The data are presented as mean ± SD and analysed using GraphPad Prism 9.0 software. The differences among the multiple groups were analysed by one-way analysis of variance. $p < .05$ was deemed a statistically significant difference.

## Results

### *Network Pharmacological Prediction*

The target genes of BER and SAE were mapped. A total of 20 genes were mapped, and the protein interaction network was constructed using STRING (Figure 1A and 1B).

GO pathway enrichment analysis was performed, and 6,076 entries were obtained by screening, among which 614 entries were molecular function (MF), 384 were cellular component (CC) and 5,078 were biological process (BP), of which the biological functions related to SAE were mainly enriched in biological processes, such as the response of cells to chemical stress, the response of cells to nitrogen compounds, the positive regulation of cell migration, the positive regulation of cell death, the response of cells to abiotic stimuli and the response of cells to nutrients (Figure 1C).

Pathway enrichment analysis was performed in the KEGG database, and the top-ranked pathways were extracted according to the *p* value. In-depth analysis of the PI3K/Akt signalling pathway revealed that the network contained key genes belonging to the PI3K/Akt signalling pathway, such as CDKN1A, CDKN2B, mTOR, NFKB1, CDK6, CDK4 and CDK2, which suggests that BER may be able to treat SAE by regulating the PI3K/Akt signalling pathway (Figure 1D).

In conclusion, BER could act on SAE through PI3K/Akt signalling pathway, insulin resistance, hepatitis and tumour pathway, and so on.

### *BER Significantly Reduced the Level of Oxidative Stress and SAE Injury*

The levels of TNF-α, IL-1β, IL-6 and IL-10 were significantly higher in the SAE group when compared with the Con group and significantly lower in the BER group when compared with the SAE group, and the effect was stronger in the BER-H group than in the BER-L group. The levels of TNF-α, IL-1β, IL-6 and IL-10 were significantly higher in the 3MA group when compared with the BER-H group (Figure 2A).

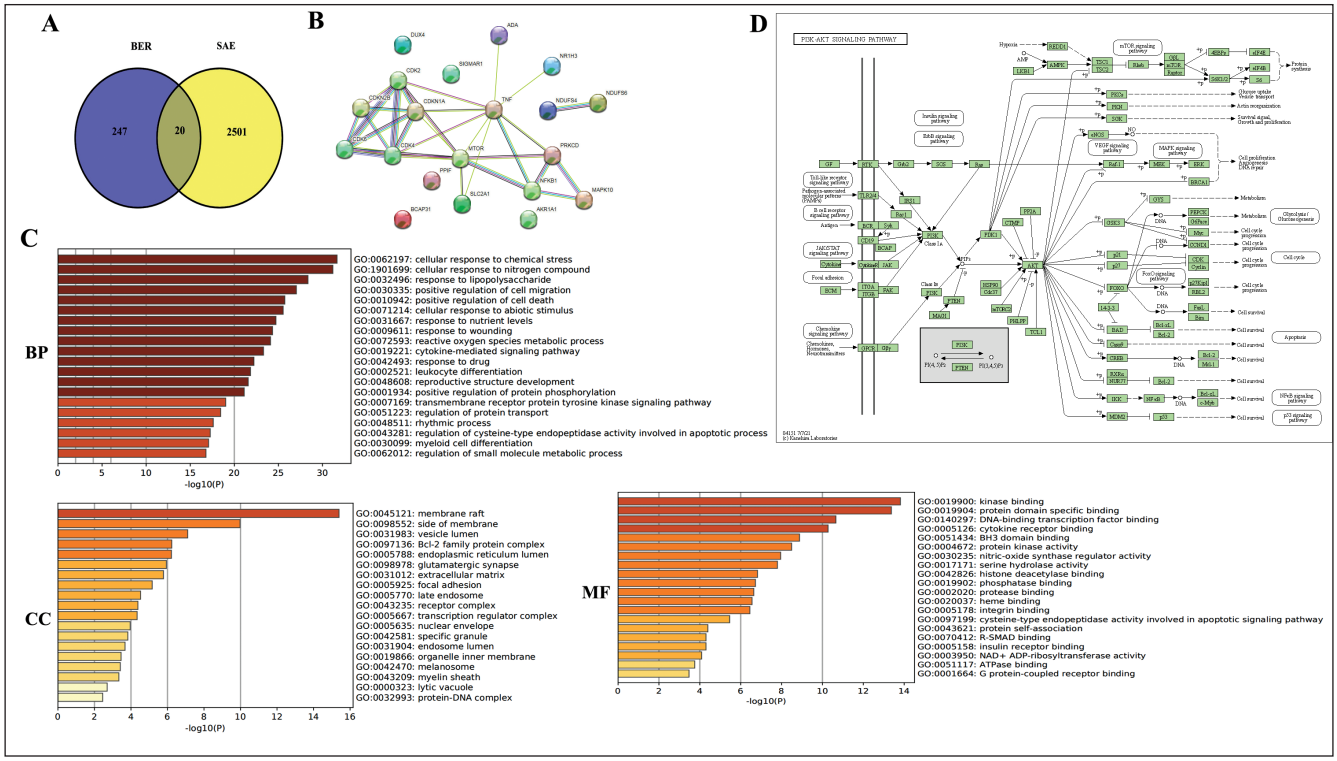



**Figure 1.** (A) Venn Diagram of BER–SAE. (B) Network Diagram of BER–SAE Interactions. (C) Enrichment Analysis Diagram of the Top 20 Signalling Pathways of BER–SAE GO. (D) With BER–SAE in the PI3K-Akt Signalling Pathway.

**Note:** BER: Berberine; GO: Gene Oncology; PI3K: Phosphatidylinositol-3 kinase; SAE: Sepsis-associated encephalopathy.

HE staining and Nissl staining showed that brain damage was significantly reduced in the BER group as compared to the SAE group. This suggested that BER could prevent I/R-induced myocardial injury by promoting autophagy (Figure 2B and 2C).

In conclusion, BER could reduce SAE injury. The autophagy inhibitor 3MA also attenuated SAE injury, suggesting that SAE injury is related to the PI3K signalling pathway.

## *BER Attenuates Brain Damage by Promoting Autophagy*

The TUNEL method specifically detects DNA breaks generated during apoptosis. Green fluorescence indicates TUNEL-stained positive cells, and it can be seen that there are fewer apoptotic cells in the BER group than in the SAE group and more apoptotic cells in the 3MA group than in the BER-H group (Figure 3A).

Transmission electron microscopy for detecting autophagy is based on identifying the structure of autophagosomes, which is the most direct and classical method for observing the autophagy phenomenon. It can be clearly seen that the BER group has fewer autophagosomes than the SAE group, and the 3MA group has more autophagosomes than the BER-H group (Figure 3B).

The results of the western blotting experiments demonstrated a decrease in the levels of PI3K, MTOR, MMP-9 and p62 in the BER group when compared to the SAE group. Conversely, the levels of Beclin1 and LC3 were found to be elevated in the BER group. In addition, the levels of PI3K, MTOR, MMP-9 and p62 in the 3MA group were found to be increased when compared to the BER group. However, this increase was not significant. Furthermore, the levels of PI3K, MTOR, MMP-9 and p62 in the 3MA group were found to be reduced when compared to the BER group. Finally, the levels of MTOR, MMP-9 and p62 in the 3MA group were found to be increased when compared to the BER group, while the level of Beclin1 and LC3 were decreased. (Figure 3C).

In conclusion, BER can alleviate autophagy-induced SAE damage. The autophagy inhibitor 3MA also alleviated SAE damage, indicating that SAE damage is associated with the PI3K signalling pathway.

## Discussion

The PI3K-Akt signalling pathway was predicted using network pharmacology. Considering that the PI3K-Akt signalling pathway has multiple downstream signalling pathways and that the pathophysiological characteristics of SAE mainly focus on neuronal damage caused by autophagy, the PI3K/

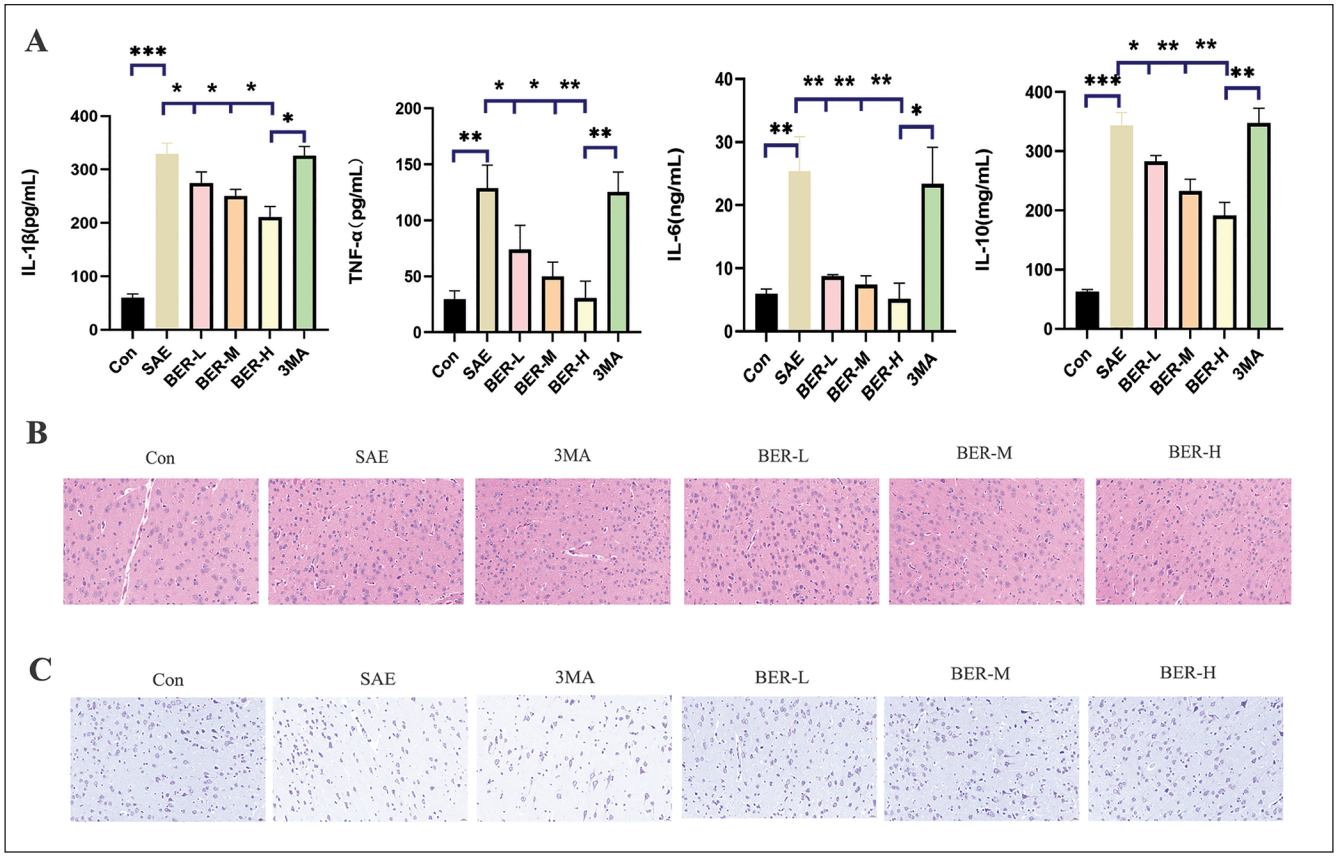



**Figure 2.** (A) Detection of TNF-α, IL-1β, IL-6 and IL-10 by Enzyme-linked Immunosorbent Assay (ELISA), (B) Hematoxylin-eosin (HE) Staining and (C) Nissl Staining.

**Notes:** $n = 3$. Data are expressed as $\bar{x} \pm s$. Significance was calculated using *t*-test. $p < .05$ was considered statistically significant $^{*}p < .05$, $^{**}p < .01$ and $^{***}p < .001$. BER: Berberine; IL-6: Interleukin-6; IL-10: Interleukin-10; IL-1β: Interleukin-1β; SAE: Sepsis-associated encephalopathy; TNF-α: Tumour necrosis factor-α.

mTOR/autophagy signalling pathway was selected in combination with BER's own pharmacological effects to ameliorate BER-induced SAE injury. Animal experiments were conducted to establish an SAE mouse model by intraperitoneal injection of lipopolysaccharide (LPS), to study the transgenic pathological changes of BER in SAE mice and to eliminate BER's effect by the autophagy inhibitor 3MA. Transmission electron microscopy was used to observe the formation of neuronal autophagy, and protein expression was detected by Western blot to explore the mechanism of action. The present study employs experimental evidence. It is hypothesised that BER has the capacity to reduce SAE injury. The autophagy inhibitor 3MA also attenuated SAE injury, suggesting that SAE injury is related to the PI3K signalling pathway.

BER can exert its anti-inflammatory and neuroprotective effects by up-regulating the expression of the inflammation-suppressing gene NR4A1 (Venu et al., 2021). BER pre-treatment can reduce inflammation and apoptosis during cerebral ischaemia–reperfusion in rats by activating the SIRT1 pathway (Yang et al., 2022). BER attenuated LPS-induced brain histopathological damage in a dose-dependent manner, inhibiting LPS-induced apoptosis, oxidative stress, inflammation and NF-κB activation (Guldenpfennig et al., 2023). BER inhibited advanced glycation end-products (AGE)-induced activation of mouse microglia (Twarda-Clapa et al., 2022). Its effect may be related to the NF-κB-mediated inflammatory signalling pathway. BER protects the blood–brain barrier against oxygen-glucose deprivation and reoxygenation (OGDEN/R) injury by inhibiting NF-κB entry into the nucleus, reducing the release of inflammatory factors and improving OGD/R-induced damage in rat brain microvascular endothelial cells (rBMECs; Ma et al., 2024). BER inhibits the expression of MCP-1 and P38MAPK pathway proteins in the hippocampal region of the brain of vascular dementia (VD) rats, thus improving one of the molecular mechanisms of learning and memory in VD individuals (Robbins et al., 2021). BER and rhubarbic acid can exert their anti-inflammatory effects by down-regulating the expression of TLR2/NF-κB signalling pathway molecules, thereby inhibiting the production and release of inflammatory factors in LPS-induced macrophages (Arya et al., 2021).

After being absorbed into the bloodstream, BER enters the brain and is taken up by neuronal cells, primarily in the hippocampus, cortex and striatum. PI3K consists of a

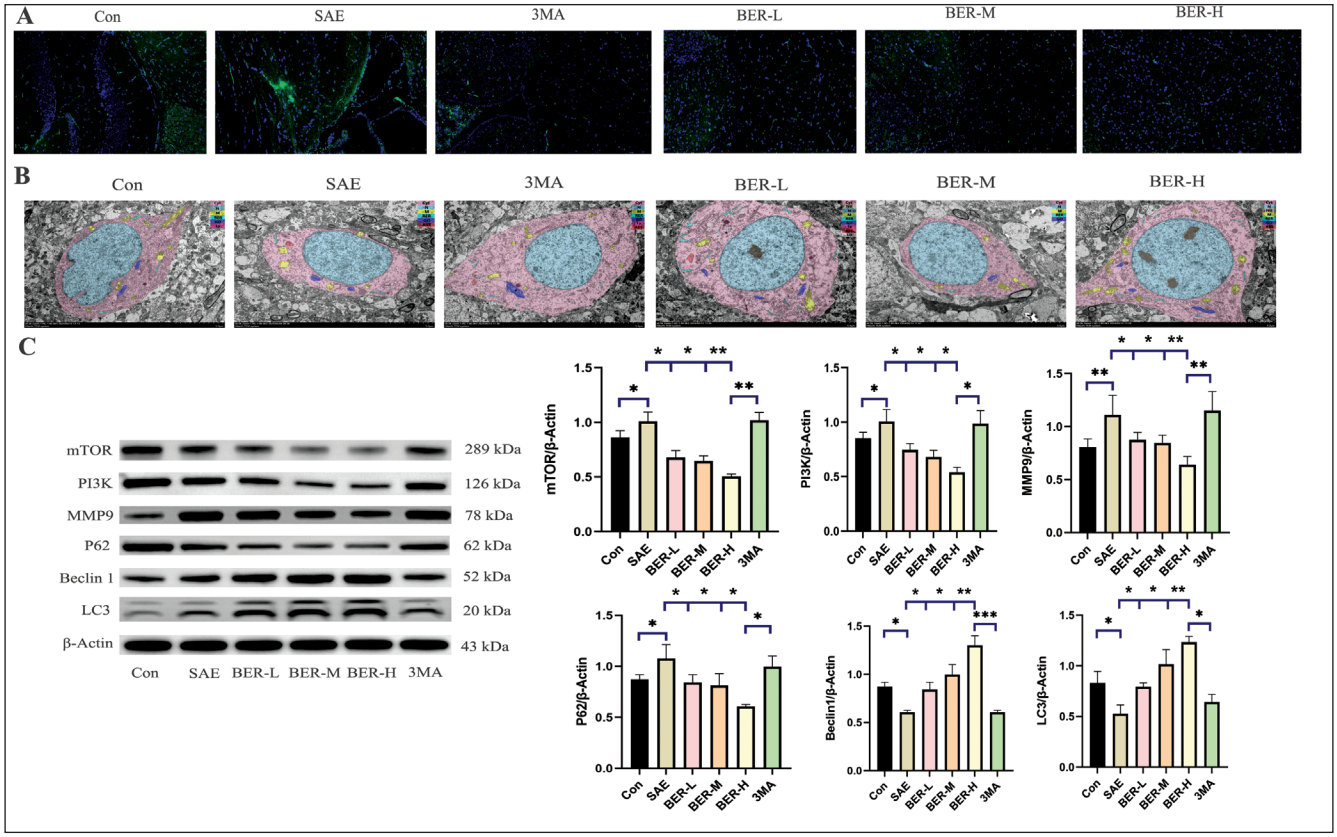



**Figure 3.** Regulation of PI3K-Akt by Berberine (BER) in Mice. (A) Terminal deoxynucleotidyl transferase dUTP nick end labelling (TUNEL) staining for apoptosis detection. (B) Transmission electron microscopy for detecting autophagy. (C) Western blotting regulation of PI3K-Akt in mice.

**Notes:** Data are expressed as $\bar{x} \pm s$. Significance was calculated using a *t*-test. $p < .05$ was considered statistically significant. *$p < .05$ and **$p < .01$. GO: Gene Oncology; LC3: Light chain 3; mTOR: Mammalian target of rapamycin; PI3K: Phosphatidylinositol-3 kinase; SAE: Sepsis-associated encephalopathy.

regulatory subunit (p85) and a catalytic subunit (p110). The regulatory subunit contains SH2 and SH3 structural domains that interact with target proteins that have corresponding binding sites (Vasan et al., 2019). Based on the results, we speculate that BER inhibits PI3K activation when it binds to the membrane receptor. Inactivated PI3K cannot catalyse the conversion of PIP2 to PIP3. PIP3 cannot then synergise with PDK-1 to activate Akt. When Akt is inactivated, it cannot transmit signals down to mTOR. This results in the inactivation of mTOR and the activation of AMPK. Activated AMPK then catalyses the phosphorylation of ULK1 serine in the ULK1 complex, thereby promoting autophagy. The Atg12-Atg5 and LC3-II complexes then control the formation of autophagosomes, which subsequently fuse with lysosomes to form autophagolysosomes. Finally, the digestive disassembly of cellular components is completed in these autophagolysosomes.

## Abbreviations

BER: Berberine; BSA: Bovine serum albumin; GO: Gene Ontology; HE: Haematoxylin-eosin; ICUs: Intensive care units; IL-6: Interleukin-6; IL-10: Interleukin-10; IL-1β: Interleukin-1β; KEGG: Kyoto Encyclopedia of Genes and Genomes; LC3: Light chain 3; MMP-9: Matrix metalloprotein-9; mTOR: Mammalian target of rapamycin; PI3K: Phosphatidylinositol-3 kinase; SAE: Sepsis-associated encephalopathy; TNF-α: Tumour necrosis factor-α.

## Authors' contributions

Yu Li and Lin Jiang participated in conceptual design, conducting experiments, data analysis and manuscript writing; Hongxiang Wang, Shijun Tang and Wei Du conducted experiments; Yuan-Jia Yue, Dugujia Gaerma and Xing Rong conducted data analysis and Lin Jiang provided financial support for manuscript writing and final approval. All authors have read and agreed to the published manuscript version.

## Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

## Ethical Approval and Informed Consent

This experiment was approved by the Experimental Animal Ethics Committee of Xinjiang Medical University (Ethics Batch Number:

IACUC-JT-2024053146) and the date (31 May 2024) of this approval. Experimental compliance (The Animal Research: Reporting of *in vivo* Experiments [ARRIVE] guidelines). Our experiments did not include clinical trials and therefore do not require patient consent.

## Funding

The authors disclosed receipt of the following financial support for the research, authorship and/or publication of this article: This study was supported by the Natural Science Foundation of Xinjiang Uygur Autonomous Region (Grant No. 2023D01C63).

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