doi.org/10.36721/PJPS.2026.39.1.REG.14455.1

Schisantherin B exerts therapeutic effects on spinal cord injury via the PI3K/AKT signaling pathway

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Abstract: **Background**: Spinal cord injury (SCI) is a severe condition causing sensory, motor, and autonomic dysfunctions, with over 759,000 patients and 66,374 new cases yearly in China. Secondary injury, driven by inflammation and apoptosis, hinders neurorestoration, making treatment challenging. Schisantherin B (SCHB), an active component of the traditional Chinese medicine Schisandra chinensis, has anti-inflammatory and anti-apoptotic effects in cerebrovascular and neurodegenerative diseases but its role in SCI remains unstudied. **Objectives**: This study aimed to investigate SCHB's therapeutic effects on SCI and clarify its underlying molecular mechanism, focusing on the PI3K/AKT signaling pathway. **Methods**: In vitro, H_2O_2-induced PC12 cell apoptosis models were treated with different SCHB concentrations; cell viability (microplate reader), apoptosis (flow cytometry, immunofluorescence for cleaved caspase-3), and PI3K/AKT activation (immunofluorescence) were detected. In vivo, mouse SCI models (12.5g weight-drop contusion) received 15mg/kg SCHB intravenously; motor function (Basso Mouse Scale, footprint analysis), tissue damage (HE/Nissl staining), apoptosis (TUNEL staining), inflammation (ELISA for TNF-α/IL-1β/IL-6/IL-10), and PI3K/AKT activation (Western blot, immunofluorescence) were assessed. **Results**: SCHB (25μM in vitro) increased PC12 cell viability (66.15% vs. 40.86% in H_2O_2 group), reduced apoptosis (5.84% vs. 10.81%), and upregulated PI3K/AKT proteins. In mice, SCHB improved BMS scores (21/28 days post-injury), increased stride length/width, reduced spinal cord cavity size, preserved motor neurons, lowered pro-inflammatory cytokines (TNF-α/IL-1β/IL-6), elevated IL-10, and activated the PI3K/AKT pathway. **Conclusion**: SCHB exerts therapeutic effects on SCI by inhibiting inflammation and apoptosis via activating the PI3K/AKT signaling pathway, supporting its potential as a candidate for SCI treatment.

Keywords: Apoptosis; Inflammation; PI3K/AKT; Schisantherin B

Submitted on 14-04-2025 – Revised on 17-08-2025 – Accepted on 20-08-2025

INTRODUCTION

It is reported that there are 759,302 patients with traumatic Spinal cord injury (SCI) in China, with 66,374 new cases each year (Jiang *et al*., 2022). SCI can easily bring serious burden to patients (Nuechterlein *et al*., 2023; Qin *et al*., 2024). Usually caused by trauma to the spine or neck, SCI triggers secondary degeneration with circulatory problems, biochemical changes and inflammation (Sterner and Sterner, 2022). SCI often causes sensory, motor and autonomic function losses below the injury level (Anjum *et al*., 2020), along with neuropathic pain and bladder/bowel issues (Chen *et al*., 2022; Eli *et al*., 2021; Ye *et al*., 2024).

Although reducing secondary damage is vital for recovery (Pizzolato *et al*., 2021), treating SCI is hard due to severe neurological impairment (Zipser *et al*., 2022). Schisandra chinensis, a traditional Chinese medicine, has been used for ages (Yang *et al*., 2022). Its component, SchisandrinB, (SCHB), shows promise in protecting against cerebrovascular and neurodegenerative diseases, as well as in treating depression (Jia *et al*., 2023; Nasser *et al*., 2020). SCHB's effect on SCI is undetermined. So, this study used *in-vitro* and *in-vivo* models to explore its impact and mechanism.

MATERIALS AND METHODS

Reagents

Schisantherin B (≥98%, Solarbio, China); hydrogen peroxide (30%, Sigma, USA); DMSO (99.90%, Solarbio, China); paraformaldehyde (95%, Sigma, USA)

Cell Culture and viability assessment

PC12 cells, a rat pheochromocytoma cell line that exhibits morphological, physiological and biochemical properties of sympathetic neurons, were obtained from the Chinese Academy of Sciences' Cell Bank. Cells were cultured at 37°C with 5% CO_2 in 25 cm^2 flasks containing DMEM (Gibco) with 10% FBS and 1% (Gibco) in a carbon dioxide incubator (Heracell™ C150i, Thermo Fisher Scientific).. Cell viability was tested by plate using a microplate reader (Epoch2, BioTek). Groups had different SCHB

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concentrations, Phosphate Buffered Saline (PBS) control, 90 μM H_2O_2 injury and H_2O_2+SCHB, measured at 450 nm.

Immunofluorescence analysis of PC12 cells

PC12 cells were seeded at 5×10^3 cells per well in 96-well plates. All experiments were performed with three biological replicates, each with five technical replicates. Three cell groups were used: control, 90 μM H_2O_2 and 90 μM H_2O_2 + 25 μM SCHB. A 0.1% DMSO vehicle was used as the control. After culturing the cells for 4 hours, we washed them with PBS. Cells were fixed in 4% paraformaldehyde, permeabilized with 0.1% Triton X-100, incubated with antibodies and imaged by a confocal microscope (SP5 Ⅱ, Leica). Intensity was calculated as the mean fluorescence intensity (MFI) per cell. Background subtraction was performed by measuring the grayscale value of randomly selected cell-free regions in each image using ImageJ, which was then subtracted from the fluorescence signal. The average MFI was calculated from at least 100 cells per field.

FACS-based apoptosis assay

Wash 5×10^5-1×10^6 PC12 cells 3x with 1ml PBS, resuspend in 200μl buffer. Annexin V-FITC (10μL) was added and incubated for 15 minutes at room temperature in the dark, followed by the addition of 300 μL binding buffer and 5 μL propidium iodide (PI) for 5 minutes. Flow cytometry (NovoCyte 3130, Agilent) was performed using Novo Express (Agilent) and data were analyzed with FlowJo software (version 7.6.5; Treestar). FSC-H/FSC-A gating was used to exclude doublets and Annexin V vs. PI quadrants were defined based on unstained and single-stained controls.

Animal experiments and drug evaluations

This study used 8 - 10 - week - old C57BL/6J Nifdc mice, approved by Jinzhou Med U's Ethics Committee. Prior to SCI, mice were anesthetized with ketamine (100 mg/kg) and xylazine (15 mg/kg) (Kakuta *et al*., 2019). A contusion-induced SCI model was established using a weight-drop procedure (Yacoub *et al*., 2014), with a 12.5 g impact device causing moderate spinal cord trauma. Antibiotics were given to prevent infection and twice-daily bladder massages started from the second day post-operation.

We used 98%-pure SCHB, dissolved it in Dimethyl sulfoxide (DMSO) and diluted with saline to 1.5 mg/ml. Sham-operated mice underwent the same process without spinal cord contusion. The SCI group received daily intravenous saline injections three times, while the SCHB group received 15 mg/kg SCHB intravenously three times a day after SCI.

Motor function recovery assessment

We employed the BMS score to assess the progress of motor function recovery, as described previously (Basso *et al.*, 2006). Any discrepancies in scores were resolved by the evaluators during the assessment and the obtained averages were recorded (n = 5 mice/group). In the footprint test, black and red pigments were applied to the hind soles and arches of each specimen and the mice were allowed to walk across a paper surface. The resulting footprints were scanned and thoroughly analyzed.

Histological and immunological analyses

Staining techniques

Seven days post-SCI in rodents, mice were deeply anesthetized with pentobarbital (50mg/kg, i.p.), followed by transcardial perfusion with PBS and subsequently with 4% (w/v) paraformaldehyde in PBS. The spine was dissected and further exposed by removing muscles and connective tissues to clearly reveal the vertebrae, sacrum and inner surfaces of the ilium. Finally, euthanasia was performed by administering a lethal dose of pentobarbital (150 mg/kg). We fixed the extracted spinal cord in 4% paraformaldehyde for 24 h at 4°C and then treated it with 30% sucrose. The isolated spinal cords were paraffin-embedded and 10μm cross-sections were made.

Several high-magnification fields were randomly selected from each section for H&E and Nissl assessment and motor neurons in each section were counted under a light microscope (BX53, Olympus). Two observers blinded to the experimental grouping independently scored each sample based on a modified Blight 5-point scale. In cases of substantial discrepancy, joint re-evaluation was performed to reach consensus. The average score per animal was used for statistical analysis to ensure representative sampling, blinded evaluation and minimization of subjective bias. For TUNEL staining, tissue samples were washed, fixed in 4% PFA, treated with Triton X-100, stained, counter-stained with DAPI and observed.

Western blot

Load 50 μg protein samples per group. Separate by SDS - PAGE, transfer to PVDF membranes, block with BSA, and incubate with primary and secondary Abs for β-actin quantification.

Immunofluorescence

Tissue specimens were prepared as described previously. After a 15-minute treatment with 0.5% Triton X-100 for dehydration and permeabilization, 5% goat serum blocked non-specific binding for 2 h. Incubation with primary Abs overnight and secondary Abs for 2 h was followed by DAPI nuclear counter-staining for microscopic visualization (SP5II, Leica).

ELISA

Spinal cord tissues were ground in saline and centrifuged to collect the supernatant. Immediately after collection, tissues were placed on ice and mechanically homogenized

in ice-cold PBS/0.1% Triton X-100 lysis buffer containing protease inhibitors, then centrifuged at 4 °C to remove debris; the resulting supernatants were used for ELISA. According to the ELISA kit instructions (Wuhan Servicebio), the supernatant was reacted with and absorbance was measured at 450 nmusing a microplate reader (Multiskan FC, Thermo Fisher).

Statistical analysis

We used GraphPad Prism v8.0 for stats. Data are shown as mean ± SD. Apply one-way ANOVA (Bonferroni) for equal variances, Kruskal-Wallis otherwise and two-way ANOVA for BMS scores. $P < 0.05$ is significant.

RESULTS

The protection of SCHB on cell viability and inhibition of apoptosis

To determine an appropriate treatment dose, we assessed the effects of various concentrations of SCHB on PC12 cell viability. The results demonstrated that there was no significant toxicity to PC12 cells when the SCHB concentration remained below 50 μM. However, when the concentration exceeded 100 μM, the viability of the PC12 cells was affected.25 μM SCHB, the cell survival rate exceeded 98%. Furthermore, when they were incubated with 90 μM H_2O_2 for 4 hours, the cell activity decreased to approximately 40.86% ($P < 0.01$) of the normal level. 25 μM SCHB, the highest cell survival rate was 66.15% ($P < 0.01$, fig. 1A).

Considering these findings, 25 μM SCHB was selected as the experimental concentration. Immunofluorescence showed that the SCHB group had a more significant decrease in Cleaved Caspase3 levels than the H_2O_2 group ($P < 0.01$, fig. 1B - C). Flow cytometry analysis revealed that the SCHB group had a lower apoptotic cell percentage (5.84%) than the H_2O_2 group (10.81%) ($P < 0.01$, fig. 1D - E), suggesting SCHB protected against nerve cell apoptosis.

SCHB Activates PI3K/AKT Signaling in-vitro

Immunofluorescence in PC12 cells reveals SCHB upregulates PI3K/AKT pathway proteins compared to the H_2O_2 group ($P<0.05$, fig. 2A- D).

SCHB mitigates tissue injury and facilitates motor function restoration

We assessed motor function using BMS scoring and footprint analysis. SCHB - treated mice had higher BMS scores at 21 and 28 days ($P < 0.01$). Footprint analysis confirmed increases in hindlimb stride, stride length and step width in the SCHB group ($P < 0.05$, fig. 3A-C). SCHB-treated mice exhibited higher BMS scores than the untreated SCI group ($P < 0.01$, fig. 3D). Tissue morphology revealed the SCHB treatment group had better tissue integrity (fig. 3E).

SCHB ameliorates SCI-induced tissue damage and inhibits apoptosis in-vivo

Using H&E and Nissl staining, we observed histological changes in mice across different groups. As illustrated in the figure4A, H&E staining revealed a cavity region surrounding the injury site. SCHB aids spinal cord repair. At 28 days, SCHB reduced cavity size and kept the spinal cord more intact ($P < 0.05$, fig. 4A, B, E, F). Nissl staining showed more ventral horn motor neurons in the SCHB group ($P < 0.01$, fig. 4C, 4G). TUNEL assay revealed fewer motor function recovery.

SCHB suppresses microglial activation and alleviates inflammation

Immunofluorescence assays showed that SCI increased the expression of (a microglia marker), but SCHB treatment decreased it, suggesting inhibition of microglial activation and proliferation ($P < 0.05$, fig. 5A, C). ELISA revealed that SCI led to high levels of.

SCHB activates PI3K/AKT signaling

Levels of PI3K proteins were higher in the SCHB group than the SCI group ($P < 0.05$, fig. 6A - G), confirming pathway activation.

DISCUSSION

SCI is a severe impairment that results in the disruption of neural signal transmission (Wang *et al.*, 2021; Ye *et al.*, 2024). The pathogenesis of SCI involves a dynamic interplay of intricate events and encompasses a multitude of biochemical cascade reactions, often referred to as secondary injury (Hachmann *et al.*, 2021; Lv *et al.*, 2021). During secondary injury, inflammation and cellular apoptosis exert substantial effects (He *et al.*, 2022; Hu *et al.*, 2022).

Following SCI, cytokines and chemokines released by microglia, astrocytes and peripheral-derived macrophages (PDMs) are transported to the injury site, triggering an inflammatory response in the affected region (Pang *et al.*, 2022). The levels of inflammatory cytokines, primarily secreted by microglia, including TNF-α, IL-1β and IL-6, are noticeably increased after injury (Zhai *et al.*, 2021). These inflammatory mediators can induce immediate cellular damage, tissue edema, elevated reactive oxygen species production and increased vascular permeability, ultimately reducing blood flow to the affected area and increasing the extent of damage.

The inflammatory response is crucial as it helps clear debris and tissue repair at the damaged site. However, overabundant inflammatory mediators, along with immune cell hyper activation, can lead to additional neuronal death and tissue degradation, obstructing axonal growth and impeding neural repair post-SCI (Chen *et al.*, 2023). ELISA results showed that SCHB reduced the levels of.

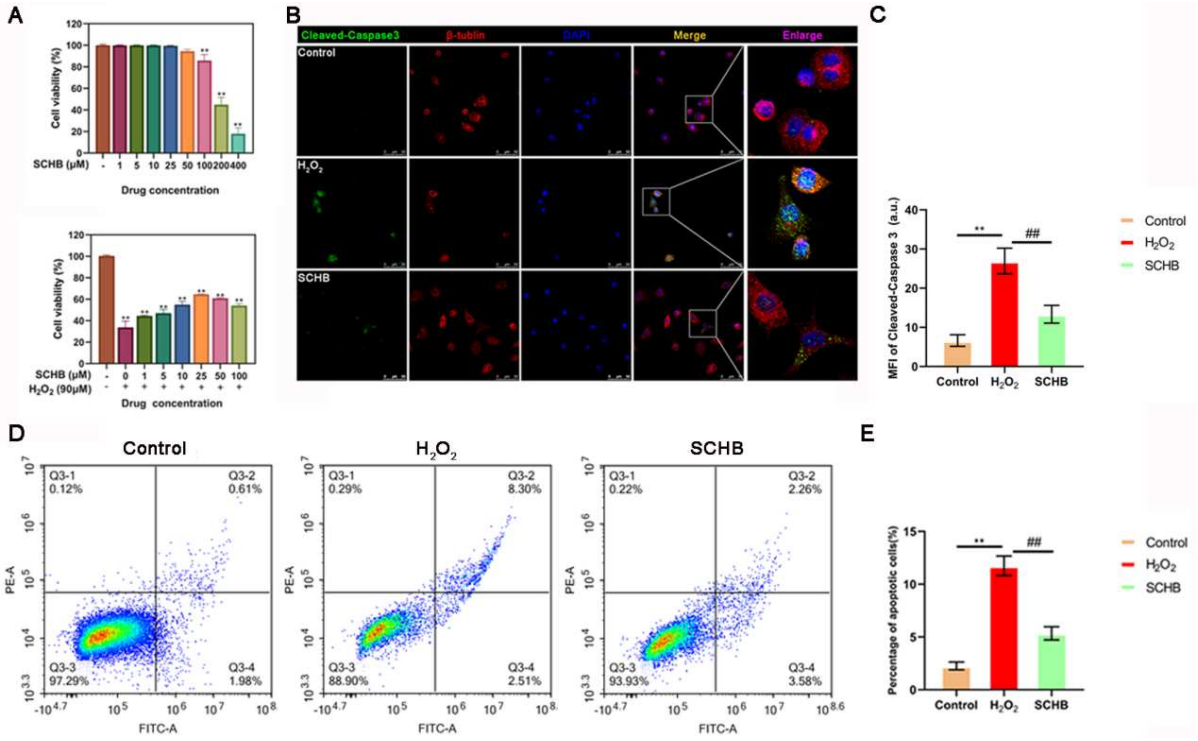

Fig. 1: SCHB significantly alleviates H2O2-induced neuronal apoptosis. It provides data on cell viability (A), levels of cleaved caspase-3 (B), and apoptotic rate (D), with highly significant differences (C, E) ($P < 0.01$, n=5).

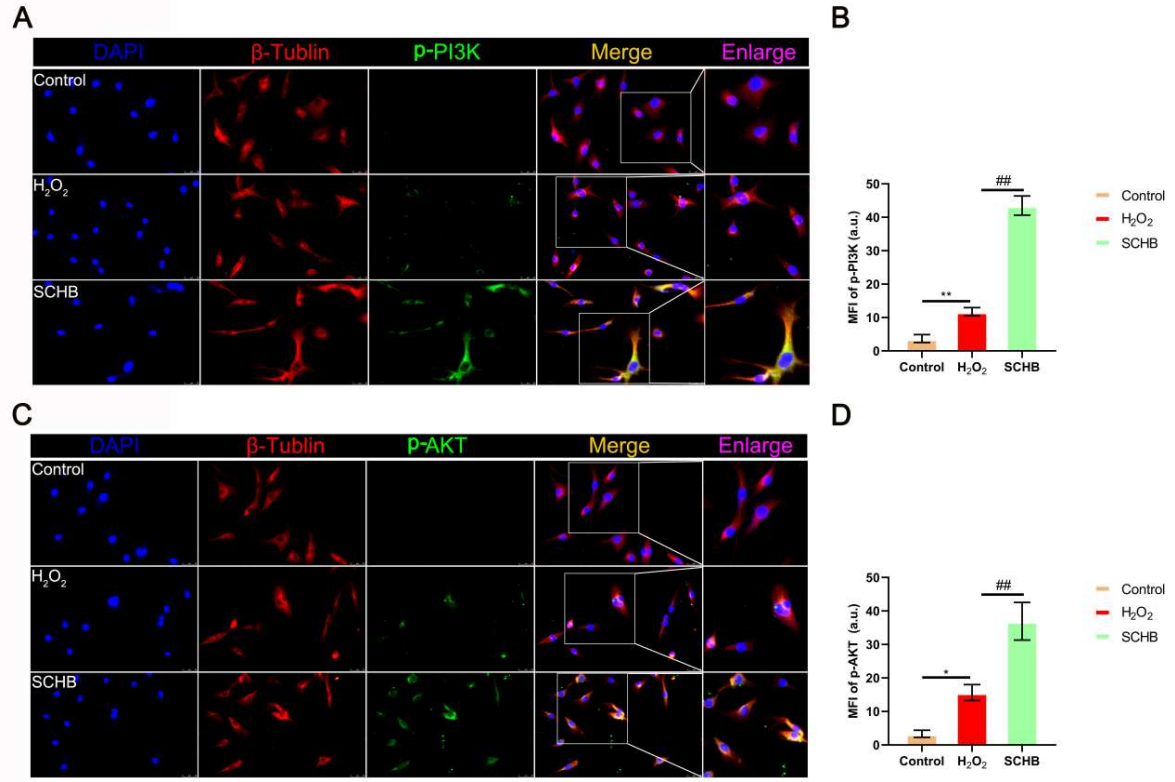

Fig. 2: SCHB activates the PI3K pathway in H2O2-treated PC12 cells (A). Images and analysis of p-PI3K show significant differences (*$P < 0.05$, **$P < 0.01$, ##$P < 0.01$, n=5) (B). SCHB activates the AKT pathway in H2O2-treated PC12 cells (C). Images and analysis of p-AKT show significant differences (*$P < 0.05$, **$P < 0.01$, ##$P < 0.01$, n=5) (D). (D).

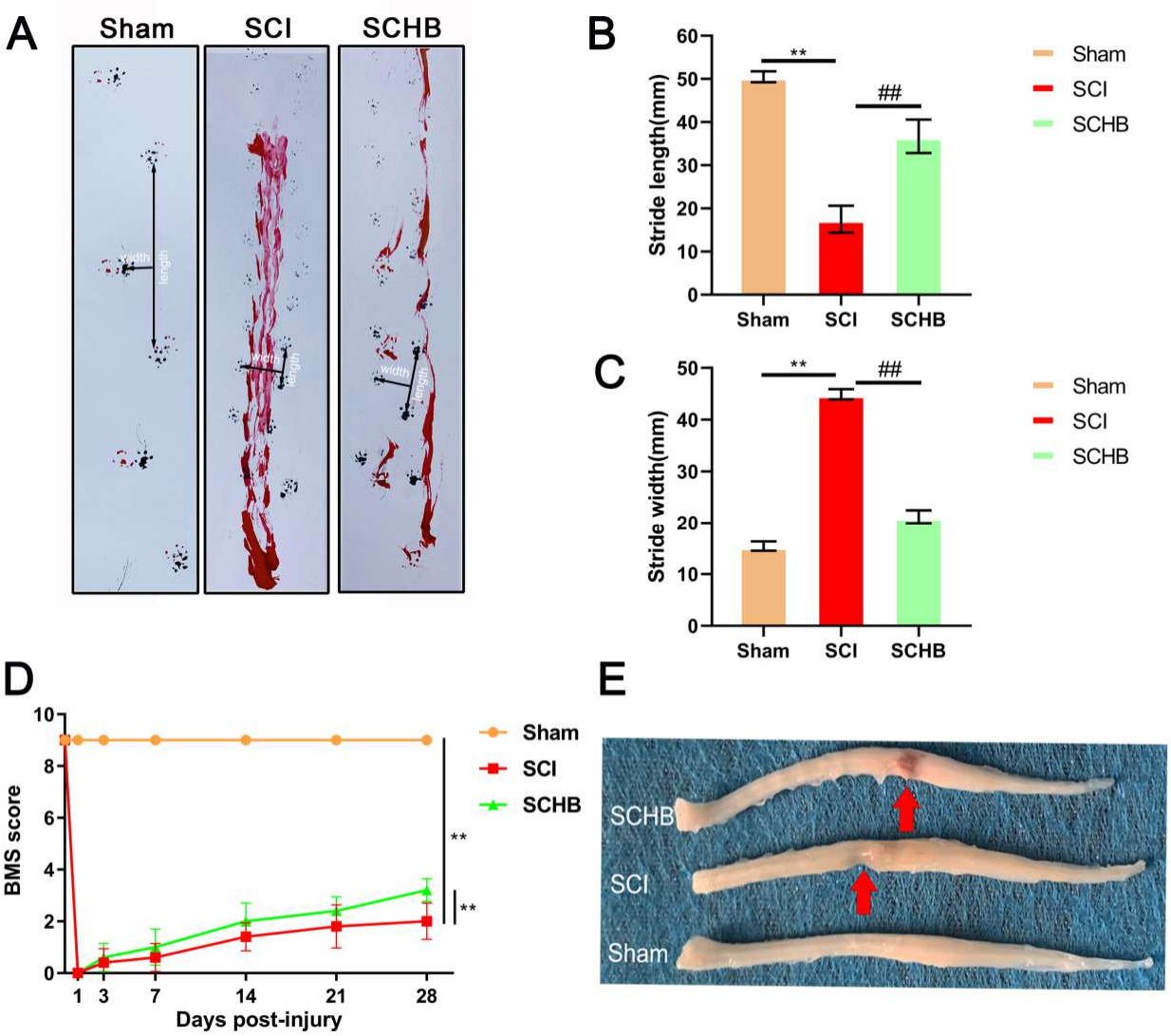

Fig. 3: SCHB can enhance post - SCI motor function. (A) Ink - blot detected mouse gait after SCHB treatment. (B) and C) Stride length and width stats post - SCHB. (D) BMS scores after SCHB. (E) Representative gross morphology of dissected spinal-cord segments. $^{**}P < 0.01$, $^{\#\#}P < 0.01$ (n=5).

However, hyper activation of inflammatory responses can lead to nerve cell death, with apoptosis playing an important role. Apoptosis is a fundamental process of cellular death that is essential for growth, maturation and tissue recovery within an organism. During the progression of SCI, apoptosis may become a predominant mode of cellular death (Shi *et al.*, 2021; Xiao *et al.*, 2023). Factors like the discharge of cytokines, oxidative stress and disease may cause neuronal damage and dysfunction. In order to stop further cellular destruction and the spread of irritation, injured cells may use apoptosis as a self-defence mechanism (Dash *et al.*, 2025). Caspase-3 plays a major role in neuronal loss following SCI and is a major caspase target of the caspase family. Important events in the process of apoptosis include DNA fragmentation in the body cell, changes in the cell membrane and the activation of intracellular signalling pathways. These morphological changes include cell contraction, membrane vesiculation and the formation of apoptotic bodies within the body. In the end, apoptosis successfully clears damaged cells, allowing for developing novel cells and tissue repair. According to the results of the current study, SCHB treatment significantly decreased Cleaved Caspase-3 appearance. Additionally, TUNEL staining was used to assess DNA fragmentation.

After SCI, SCHB significantly decreased the number of TUNEL-positive neurons. Therefore, SCHB blocks apoptosis after SCI, protecting neurons from harm. Schisandra chinensis has a significant effective component called SCHB. By excitation the PI3K/AKT/mTOR pathway, studies have demonstrated that SCHB enhanced

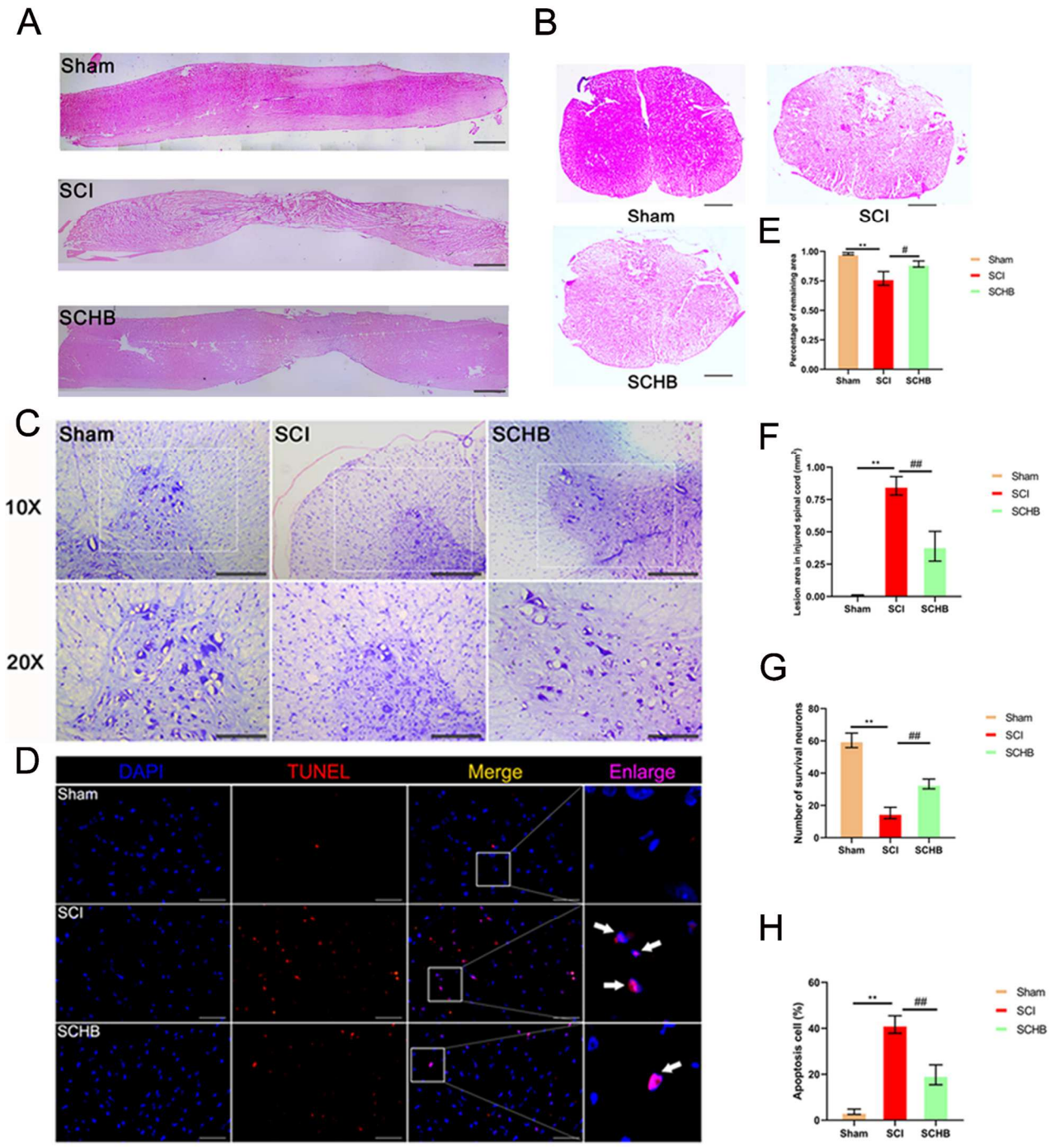

Fig. 4: Illustrates that SCHB can promote the repair of spinal cord tissue and reduce apoptosis. (A and B) Show H&E staining of the mouse spinal cord; (C) Shows Nissl staining; (D and H) Present representative TUNEL pictures and quantitative analysis; (E - H) Statistical results of pathological changes and neuronal damage ($P < 0.01$, $\#\#P < 0.01$, n=5).

Alzheimer's disease and depression's memory and mental performance (Jia *et al.*, 2023; Nasser *et al.*, 2020). A crucial signalling route for cell proliferation, differentiation and programmed cell death is the PI3K/AKT pathway. According to research, activating the PI3K/AKT pathway may help stop cellular apoptosis and the inflammatory response. The PI3K/AKT signalling pathway can control inflammatory mediators like cytokines (IL-6, TNF-1) and chemokines (Han *et al.*, 2023).

These elements promote the selection and recruitment of inflammatory cells in the inflammatory response. Our

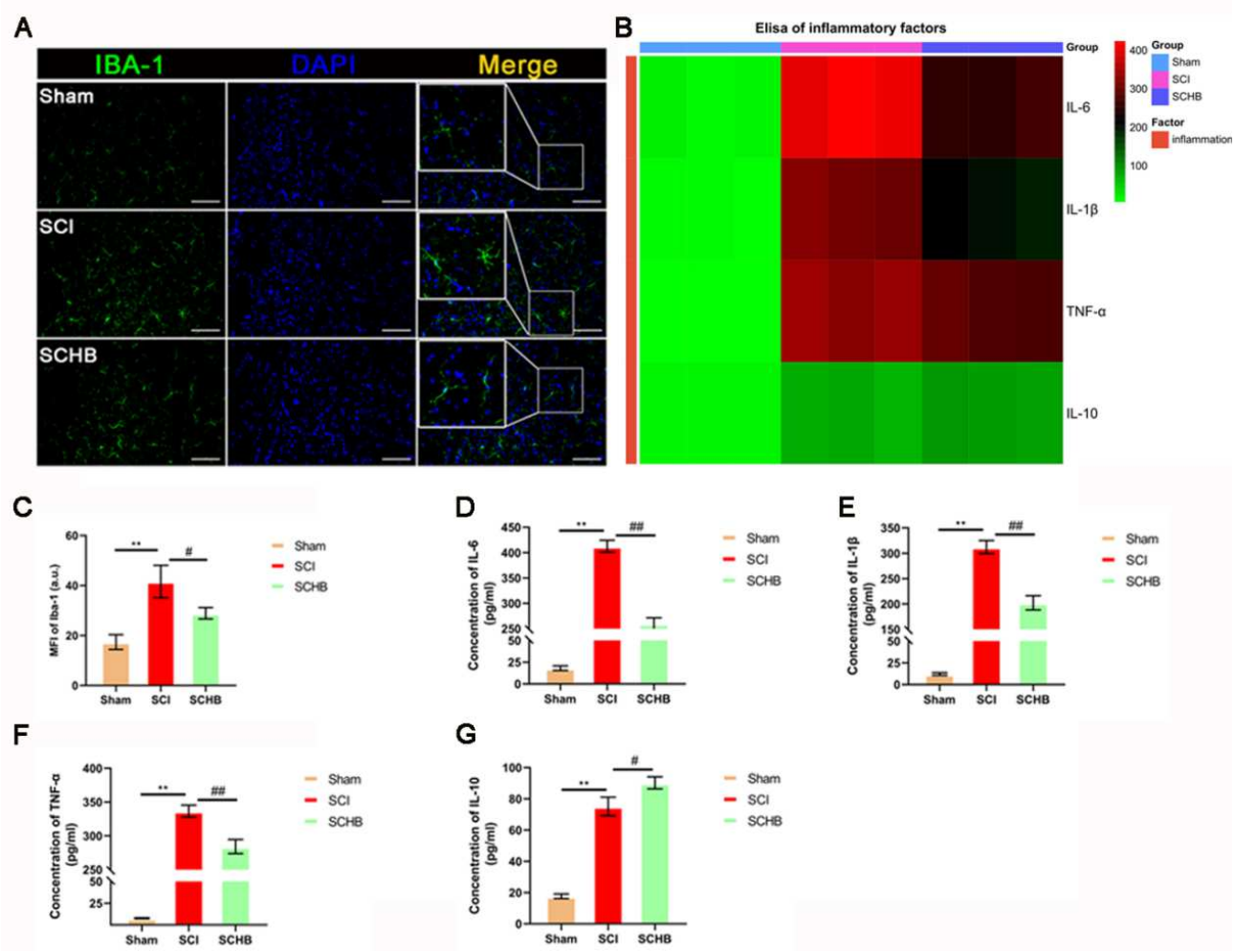

Fig. 5: SCHB alleviates inflammatory responses. This figure includes images/analysis of IBA-1 (A), a heatmap of inflammatory factors (B), and ELISA statistical results for TNF- α , IL-6, IL-1 β , and IL-10 (C-G) (**P* < 0.05, ***P* < 0.01, #*P* < 0.05, ##*P* < 0.01, n=5).

research revealed that p-AKT/AKT and p-PI3K/PI3K protein expression rates decreased after SCI. These protein expression rates increased following the administration of SCHB. Additionally, we observed a decrease in the expression of the microglia. So, we speculate that SCHB may manage apoptosis and inflammation after SCI and is related to the PI3K/Akt pathway. Consistent neuroprotective effects via PI3K/AKT modulation have been reported for several natural compounds. Ginsenoside Rg1 enhances astrocytic repair, up-regulates PI3K/AKT signaling and improves hind-limb function after SCI (Xu *et al*., 2020). Aloperine reduces oxidative stress, inflammation and apoptosis through PI3K/AKT/NF-κB pathways, leading to better locomotor outcomes (Okutan *et al*., 2025). Melatonin promotes autophagy, suppresses neuronal apoptosis and accelerates motor recovery in a rat SCI model via PI3K/AKT/mTOR signaling (Li *et al*., 2019).

Taken together with these studies, our results further highlight PI3K/AKT signaling as a shared molecular axis through which SCHB and other neuroprotective phytochemicals mitigate secondary injury and promote functional recovery after SCI. However, our current experimental design is insufficient to determine whether this activation is a direct effect of SCHB or a secondary consequence of reduced oxidative stress. We acknowledge this limitation and will address it in future studies.

CONCLUSION

In conclusion, our investigation concluded that by activating the PI3K/AKT signal channel, SCHB reduced inflammation and apoptosis following SCI. These studies suggested SCHB's possible use as a therapeutic agent for SCI.

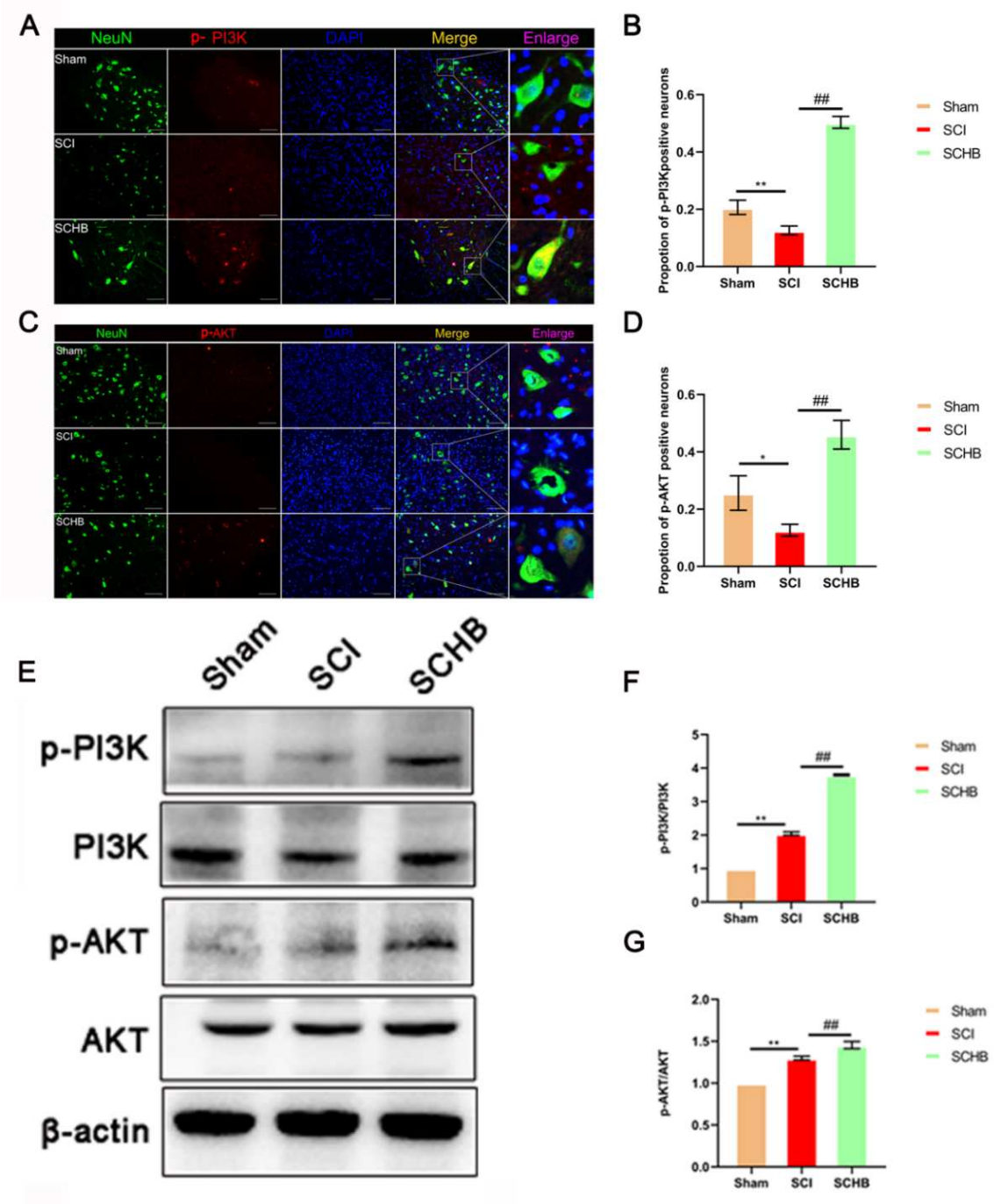

Fig. 6: Reveals SCHB further activates PI3K/AKT pathway *in-vivo*. It shows p - PI3K and p - AKT pics/analysis and their expression levels (*$P < 0.05$, **$P < 0.01$, ##$P < 0.01$, n=5).

Acknowledgement
Not applicable.

Authors' contributions
X.M., S.L. and H.T.participated in research design; J.W. and J.L. performed experiments; W.W.and H.Z. contributed to the writing of the manuscript.

Funding
This work was supported by the National Natural Science Foundation of China (Grant Nos. 82072165).

Conflict of interest
This study does not involve any conflicts of interest.

Ethical approval
This study was conducted after approval by the Ethics

Committee of Jinzhou Medical University (No. 230516) and in accordance with the 'Guide for the Care and Use of Laboratory Animals' provided by the National Institutes of Health (NIH).

Data availability statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on request.

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