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The neuroprotective effect of *Salvia przewalskii* extract of total phenolic acids for the treatment of acute spinal cord injury in rats

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Abstract: *Salvia przewalskii* Maxim. is a traditional Chinese herbal medicine which has long been used for the treatment of cardiovascular diseases in China. The current study aimed to investigate the neuroprotective effect of *Salvia przewalskii* extract of total phenolic acids (SPE) in a rat model of acute spinal cord injury (ASCI). Quantitative analysis of the active constituents in SPE by HPLC showed that rosmarinic acid accounted for 34.32% and salvianolic acid B for 4.27%. The experiment with the ASCI rat model demonstrated that SPE did not have significant adverse effects on body mass on day 1 and 3 after drug administration. In addition, SPE treatment significantly enhanced the BBB scores, improved the inclined plane angles and increased the serum levels of oxidative stress markers SOD and GSH in ASCI rats. Concurrently, it reduced the serum levels of MDA and inflammatory cytokines TNF-α, IL-1β, IL-6, IL-17 and IL-18. SPE also mitigated neuronal damage within the spinal cord tissue by minimizing hemorrhage and preserving neuronal integrity. Mechanistically, SPE ameliorated neuronal damage in the spinal cord by attenuating oxidative stress and inflammatory responses, thereby facilitating the recovery of motor function in ASCI rats.

Keywords: Acute spinal cord injury; Inflammatory; Neurological function; Neuroprotective effect; Oxidative stress; *Salvia przewalskii* extract of total phenolic acids

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INTRODUCTION

Acute spinal cord injury (ASCI) denotes abrupt impairment to spinal cord function resulting from trauma, infection, inflammation, or specific autoimmune factors. It represents a devastating, incapacitating and potentially life-threatening condition which frequently gives rise to diverse complexities, adversely impacts the psychosomatic well-being and the quality of life of patients, or even threatens their lives (Srinivas *et al*., 2017). Initial management primarily entails decompression surgery. However, there is currently a dearth of specific drugs for symptomatic relief in clinical settings. The identification and validation of pharmaco-therapeutic agents suitable for early intervention of ASCI to attenuate secondary damage have emerged as a focal point and challenge in the clinical research domain of the disease.

Salvia przewalskii Maxim. is a perennial herb belonging to *Salvia* genus in the Lamiaceae family. It is primarily distributed in the southwestern regions of Gansu, Sichuan, Yunnan and Tibet provinces in China (Editorial Committee of Chinese Academy of Sciences, 1977). *S. przewalskii* is a substitute for the traditional Chinese medicine Danshen (Salviae Miltiorrhizae Radix et Rhizoma) in China (Zhao *et al*., 2024; Chen *et al*., 2025). Both *S. przewalskii* and *S. miltiorrhiza* Bge. belong to the same botanical genus. *S. miltiorrhiza* acts as the principal botanical origin of the extensively employed traditional Chinese medicine Danshen (Zhao, 2003). The roots and rhizomes of *S. przewalskii* are extensively employed in folk medicine for their efficacy in regulating menstruation in that they can enhance blood circulation, resolve stasis, sedate and relieve pain, particularly in the treatment of cardiovascular diseases and liver ailments (Nanjing University of Chinese Medicine, 2006; Qiu *et al*., 2022). The primary chemical constituents of *S. przewalskii* consist of lipid-soluble diterpenoids, triterpenoids, anthraquinones and water-soluble phenolic acids (Guo *et al*., 2025). The lipid-soluble diterpenoids encompass danshenone I, danshenone IIA, danshenone IIB, cryptodanshinone, dihydrodanshinone and hydroxydanshinone. In contrast, the water-soluble phenolic acids include protocatechuic acid, caffeic acid, rosmarinic acid, lithospermic acid and salvianolic acid B. (Yang *et al*., 2008; Hong *et al*., 2023). Notably, przewaquinone A, a diterpene quinone isolated from *S. przewalskii* Maxim. var. mandarinorum (Diels) Stib, inhibits angiotensin II-induced endothelial diastolic dysfunction through AMPK activation and suppression of melanoma cell growth by inhibiting STAT3 signaling and inducing autophagy (Chen *et al.*, 2024; Jiang *et al.*, 2025). Furthermore, przewaquinone A has been shown to possess neuroprotective effects (Jiang *et al.*, 2025). Our research team has conducted comprehensive investigations on *S. przewalskii* employing a macroporous adsorption resin column chromatography process for the preparation of

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Salvia przewalskii extract of total phenolic acids (SPE) from the ethanol total extract of Salvia przewalskii Radix et Rhizoma medicinal materials and established the quality standards of SPE using various contemporary pharmaceutical analysis techniques (Li *et al*., 2014; Yang *et al*., 2015). Previous investigations have demonstrated that SPE effectively reduces whole blood viscosity in rats and enhances blood circulation (Yang *et al*., 2012). Both *in vivo* and *in vitro* investigations have verified the protective properties of SPE against ionizing radiation-induced injuries in rats and damage to vascular endothelial cells caused by ionizing radiation exposure (Yang *et al*., 2020; Hong *et al*., 2021). The primary objective of this study was to evaluate the neuroprotective properties of SPE on neurological function following ASCI in rats and explore the underlying action mechanism *in vivo* for the sake of laying a robust theoretical foundation and providing experimental evidence for the utilization of SPE in the treatment of ASCI.

MATERIALS AND METHODS

Reagents and instruments

Reagents used in this study included the reference substance of rosmarinic acid (purity ≥97%; batch No. L2108770) and salvianolic acid B (purity >98%; batch No. A2403260) (Aladdin Biochemical Technology Co., Ltd., Shanghai, China); rat serum superoxide dismutase (SOD), glutathione (GSH) and malondialdehyde (MDA) Elisa kits (Nanjing Jiancheng Bioengineering Institute Co., Ltd., Nanjing, China; batch No. 20240721, 20240828 and 20240617); rat serum tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6 and IL-18 Elisa kits (Beijing Merida Technology Co., Ltd., Beijing, China; batch No. 20240205, 20240202, 20240207 and 20240206); and IL-17 Elisa kits (Shanghai Fankew Biological Technology Co., Ltd., Shanghai, China; batch No. F2212-A). Water was subjected to double distillation prior to use. All other reagents were of analytical grade from China Sinopharm Chemical Reagent Co., Ltd (Beijing, China).

Instruments used in this study were SQP Quintix 124-1CN electronic analytical balance with a maximum load capacity of 120 g and a readability of 0.1 mg (Sartorius Corporation, Germany); MP3002 electronic balance, with a maximum load capacity of 300 g and a readability of 10 mg (Shanghai Sunny Hengping Scientific Instrument Co., Ltd., China); High performance liquid chromatography (HPLC) system (Nexera-i LC-2040C 3D$^+$) with a SPD-40V diode array detector (Shimadzu Corporation, Japan); RM2016 pathological slicer (Shanghai Leica Instruments Co., Ltd.); and Eclipse C1 upright bright field microscope (Nikon Corporation, Japan).

Experimental drugs

Self-prepared SPE (batch No. 20220606) was homogeneously dispersed in a 1% sodium carboxymethyl cellulose (CMC-Na) solution to generate SPE suspension solutions at concentrations of 5 mg/mL, 10 mg/mL and 20 mg/mL. Methylprednisolone sodium succinate (MP) for injection (batch No. EM8116, each vial containing 500 mg of methylprednisolone) was sourced from Pfizer Manufacturing Belgium NV. Prior to use, MP was dissolved in water for injection to achieve a 25 mg/mL MP solution. The blank control solution was a 1% CMC-Na aqueous solution. Both solutions were refrigerated and allowed to equilibrate at room temperature before administration.

Quality control of the experimental drugs

The bioactive constituents rosmarinic acid and salvianolic acid B in SPE were quantitatively analyzed utilizing a modified HPLC method developed by our research team (Li *et al*., 2014).

Experimental animals

A total of 72 male Sprague-Dawley rats (License No. SCXK (Su) 2021-0013 and Certification No. 202241779) weighing 200-240 g (Cavens Experimental Animal Co., Ltd., Changzhou, China) were housed in a controlled animal facility, where they were provided with a standard rodent diet, unrestricted access to water and opportunities for physical exercise. The animals underwent 3-day acclimatization prior to commencing the experiment.

Methods of animal experiments

Modeling method: Following a 12-h fasting period, 72 rats were equally randomized to six groups: sham surgery group (N group), injury model group (M group), positive control group receiving methylprednisolone (MP group) and three groups receiving low-, medium- and high-dose SPE (designated as SPE1, SPE2 and SPE3 group). Body mass was measured using an electronic balance and anesthesia was induced via intraperitoneal injection (*i.p.*) of 1% sodium pentobarbital at a dosage of 40 mg/kg of body mass. After successful induction of anesthesia, the rat was positioned in a prone stance on the surgical frame. The dorsal area was clipped and thoroughly prepared, followed by antiseptic treatment of the skin with iodine solution. A longitudinal incision was made along the midline of the back to expose the skin layer, subcutaneous tissue and fascia sequentially. The paraspinal muscles were bluntly dissected to completely reveal the T9-T11 vertebral laminae. The T10 vertebral lamina was subsequently removed using bone forceps to access the T10 segment of the spinal cord.

Rats in M, MP and SPE groups underwent spinal cord injury modeling using a modified Allen's method (Xiong *et al*., 2011). During the procedure, the soft tissues adjacent to the spinal cord were retracted and the spine was stabilized. A circular plastic spacer (diameter 3.5 mm) was placed on the surface of the T10 spinal cord following thorough disinfection with iodine. A 10 g

weight was then dropped from a height of 2.5 cm onto the T10 spinal cord and the weight was maintained in position for 3 min before removal to induce ASCI. After confirming the spinal cord injury, the incision was sutured in layers and dressed appropriately. In contrast, rats in N group underwent sufficient exposure of the T10 spinal cord without impact and the wound was sutured directly in layers and dressed. The methodology for the establishment of the ASCI rat model is depicted in Supplementary Data fig. S1.

Therapeutic method: Following surgical dressing, rats in SPE1, SPE2 and SPE3 groups were orally administered SPE solutions at concentrations of 5 mg/mL, 10 mg/mL and 20 mg/mL in the specified order, at a dosage of 10 mL/kg body mass administered once per day for three consecutive days. Rats in N and M groups received the same dose of 1% CMC-Na aqueous solution orally. Rats in MP group were administered a 25 mg/mL solution of MP via *i.p.*, with dosing and timing calculated based on the established clinical treatment protocols for ASCI patients using MP as described in the instructions (Pfizer Manufacturing Belgium NV) (National Health Commission and the National Administration of Traditional Chinese Medicine of China, 2016). The initial dose of 7.6 mL/kg body mass was administered via *i.p.*, followed by subsequent doses of 8.16 mL/kg body mass at 0.75, 6.75 and 12.75 h, and a final dose of 6.8 mL/kg body mass at 18.75 h, with no additional doses administered thereafter. For infection prophylaxis, 8×10^5 U penicillin sodium was injected via *i.p.* once daily for 3 days postoperatively. Following recovery from anesthesia, rats were housed separately and given unlimited access to food and water and assisted in bladder voiding by manual compression of the bladder three times daily until they achieved spontaneous urination.

Observation indicators

Observation of signs and body mass measurement in rats: During the experiment, daily observations were conducted to assess various parameters, including food and water intake, urination and defecation patterns and the overall mental status of rats in each group. Additionally, the body mass of rats in each group was measured daily prior to feeding.

Motor function assessment: On day 1 and 3 post-modeling, six rats from each group were selected and their body mass was measured using an electronic balance, followed by the BBB (Basso-Beattie-Bresnahan 21-point open-field locomotor evaluation scale) scoring and inclined plane test. The BBB scoring scale categorizes the functional recovery of rats into 21 progressive levels (0-21 points) by assessing their spontaneous motor behavior in an open field. It quantifies joint activity, gait coordination and fine motor skills, with a maximum score of 21 indicating normal motor function and a score of 0 representing complete paralysis. The BBB scoring was conducted according to reference (Dergham *et al*., 2002; Fournier *et al*., 2003) using a double-blind experiment method. Rats were placed in a large open area and their trunk position and stability, hind limb movement, gait, coordination, paw placement, toe spread and tail position were observed and recorded. Scores were given on both sides and then averaged. The inclined plane test was conducted according to reference (Zhang *et al*., 2012), using a double-blind experiment method. Rats were placed on a custom-made inclined plane with their body axis parallel to the axis of the plane and the head elevated towards one side of the incline. The angle of the incline was gradually increased from 0° and the maximum angle at which the rat stayed on the incline for at least 5 seconds was recorded after 3 trials and the average was calculated.

Determination of serum oxidative stress markers and inflammatory cytokines: Subsequent to the motor function assessment, rats were anesthetized as described in "*Section: Modeling method*". A thoracotomy was performed to access the heart and aorta, from which blood was collected. A minimum of 5 mL whole blood was drawn from each rat into a coagulation-promoting tube, which was gently inverted 4-5 times. The samples were permitted to clot for 30 min prior to centrifugation at 3500-4000 rpm for 10 min. After the serum had fully separated from the blood clots, it was harvested and preserved at -80°C. Following the manufacturer's guidelines, the levels of SOD, GSH, MDA, along with TNF-α, IL-1β, IL-6, IL-17 and IL-18 in the serum samples from all rat cohorts were measured.

Tissue sampling and pathological observation: After blood collection from the heart, the right atrium was cut open and 200 mL heparin saline was perfused into the left ventricle using a syringe, with the rat's body organs flushed constantly until the liver and sclera became pale. The heart was then perfused with 4% paraformaldehyde for 200 mL and fixed for 40 min. A spinal cord tissue 1.5 cm around the spinal cord injury site was taken for pathological examination.

The spinal cord tissue samples were preserved in a 4% paraformaldehyde solution for 24 h, dehydrated, cleared, paraffin embedded, serially sliced into 5-μm sections and stained with hematoxylin and eosin (H&E) to create pathological specimens. These stained sections were then analyzed using a light microscope for histopathological examination.

Statistical analysis

Experimental data were analyzed utilizing IBM SPSS version 21.0 software, with quantitative data expressed as the mean ± standard deviation (SD). One-way analysis of variance (ANOVA) was employed to evaluate differences in quantitative data across the various groups and pairwise comparisons were performed using the Tukey post-hoc test. A significance level of $P<0.05$ was considered statistically significant.

RESULTS

Main active constituents in SPE

Chromatographic conditions: Chromatographic analysis using a Shimadzu C_{18} column showed the following specifications: 4.6 mm in diameter, 250 mm in length and a particle size of 5 μm. The mobile phase comprised a combination of acetonitrile (A) and a 0.05% aqueous solution of phosphoric acid (B), utilizing a gradient elution profile as follows: from 0 to 20 min, 12% A to 20% A; from 20 to 60 min, 20% A to 30% A; and from 60 to 65 min, 30% A back to 12% A. The column temperature was maintained at 30°C and detection was carried out at a wavelength of 288 nm. The flow rate was held constant at 1.0 mL/min and a sample volume of 20 μL was injected.

Content determination results: Under the specified chromatographic conditions, rosmarinic acid and salvianolic acid B were completely separated, the retention time being 34.288 min and 42.351 min respectively. Rosmarinic acid demonstrated excellent linearity within the concentration range of 37.5 μg/mL to 750.0 μg/mL, while salvianolic acid B exhibited good linearity in the range of 22.5 μg/mL to 450.0 μg/mL. The determined content of rosmarinic acid and salvianolic acid B in SPE was 34.32% and 4.27% respectively. The chromatogram is presented in fig. 1 and the standard calibration curve is presented in fig. 2.

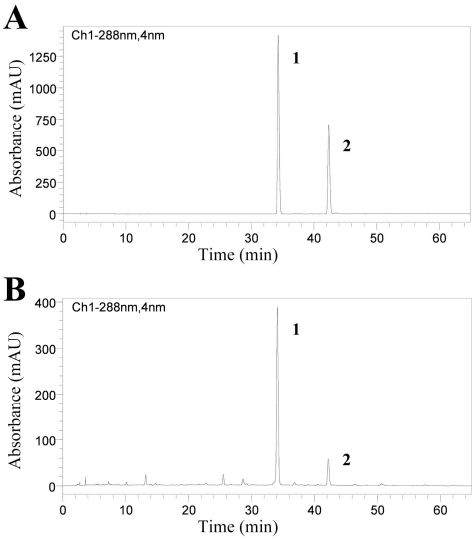

Fig. 1: HPLC chromatograms for quantification of the main active constituents in SPE.
(A) Rosmarinic acid and salvianolic acid B mixed reference substance. (B) SPE. 1. Rosmarinic acid. 2. Salvianolic acid B.

Effects of SPE on physical signs in rats

Following spinal cord injury, rats in all but N groups exhibited rhythmic jerking of the lower limbs, spasmodic tail movements and slow lifting followed by a gradual descent indicative of delayed paraplegia. The dura mater appeared intact but exhibited a purplish-red color, tautness and swelling and the spinal cord tissue at T10 level demonstrated edema and hemorrhage, indicating that the spinal cord injury model was established successfully. No such injurious symptoms were observed in the rats of N group. After 1- and 3-day treatment, the injury signs in M group showed no significant change but improved in varying degrees in MP group and all SPE treatment groups, especially in MP group and high-dose SPE group.

Effects of SPE on body mass in rats

After 1- and 3-day treatment, no significant differences in the body mass of rats were observed between the groups (all $P>0.05$). The results indicate that there was no significant reduction in the body mass of rats within 3 days following ASCI. Details are illustrated in fig. 3.

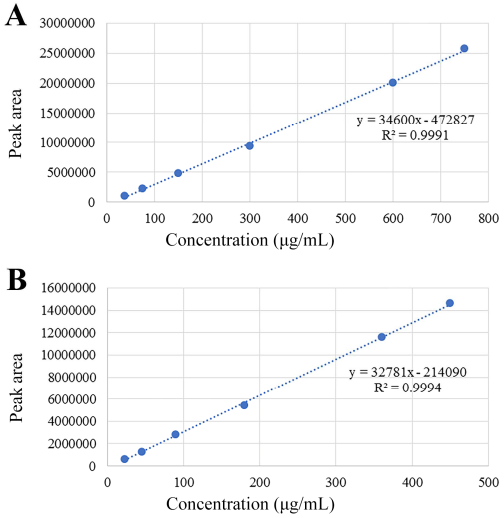

Fig. 2: Standard calibration curves for quantification of the main active constituents in SPE.
(A) Rosmarinic acid. (B) Salvianolic acid B.

Effects of SPE on BBB score and inclined plane test angle in rats

After 1- and 3-day treatment, the BBB scores and inclined plane test angles of rats in M, MP and all SPE groups were markedly lower than those observed in N group (all $P<0.0001$), indicating the occurrence of ASCI. After 1-day treatment, the BBB scores in MP group and high-dose SPE group showed a significant increase when compared to M group ($P<0.05$ and $P<0.01$). The inclined plane test angles in MP group and all SPE groups demonstrated a notable rise in comparison to M group (all $P<0.0001$). After 3-day treatment, the BBB scores and inclined plane test angles in MP group and all SPE groups were further increased relative to day 1, with significant improvements in BBB scores for MP group, medium- and high-dose SPE groups in relation to M group ($P<0.01$, $P<0.05$ and $P<0.001$). Additionally, the inclined plane test angles in MP group and all SPE groups were significantly greater than those in M group ($P<0.0001$, $P<0.01$, $P<0.001$ and $P<0.0001$).

These findings indicate that treatment with MP and medium- and high-dose SPE significantly enhanced motor function of the rats, with the efficacy of SPE being positively correlated with dosage. The enhancement in BBB scores and inclined plane test angles observed with high-dose SPE was comparable to that seen in MP (refer to fig. 4 for further details).

Effects of SPE on oxidative stress marker levels in rats

After 1- and 3-day treatment, the serum levels of SOD and GSH in M group were significantly reduced compared to N group (P<0.0001), while the serum level of MDA was significantly elevated (P<0.0001), indicating a pronounced oxidative stress response of ASCI. After 1- and 3-day treatment, the serum SOD levels in MP group and all SPE groups were significantly increased compared to M group (all P<0.0001). Additionally, the serum GSH level in high-dose SPE group was significantly elevated (P<0.05 and P<0.01). Furthermore, the serum MDA levels in medium- and high-dose SPE groups were significantly reduced compared to M group (both P<0.01) after 1- and 3-day treatment.

These findings indicate that treatment with medium- and high-dose SPE significantly elevated the serum SOD and GSH levels while markedly decreasing the serum MDA levels. Moreover, the efficacy of SPE was positively correlated with dosage and the degree of inhibition of the oxidative stress response by medium- and high-dose SPE was comparable to that of MP. The results are presented in fig. 5.

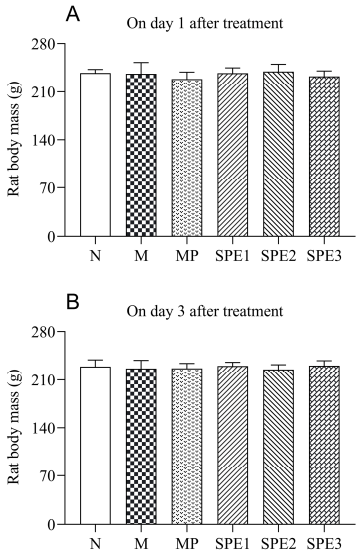

Fig. 3: Comparison of body mass in each group rats after treatment ($\bar{x}$±s, n=6).
(A) On day 1 after treatment. (B) On day 3 after treatment.

Effects of SPE on serum inflammatory cytokine levels in rats

After 1- and 3-day experiment, the serum levels of TNF-α, along with IL-1β, IL-6, IL-17 and IL-18, were significantly higher in M group than those in N group (all P<0.0001), indicating a pronounced inflammatory response in the rats. After 1-day treatment, the serum IL-1β levels in MP group and high-dose SPE group were significantly reduced compared with those in M group (P<0.0001 and P<0.001). After 3-day treatment, the serum levels of IL-1β in MP group and all SPE groups were also significantly decreased compared with those in M group (P<0.0001, P<0.01, P<0.001 and P<0.01). After 1- and 3-day drug administration, the serum levels of TNF-α, along with IL-6, IL-17 and IL-18 in MP group and all SPE groups exhibited a notable reduction in comparison to M group (all P<0.0001).

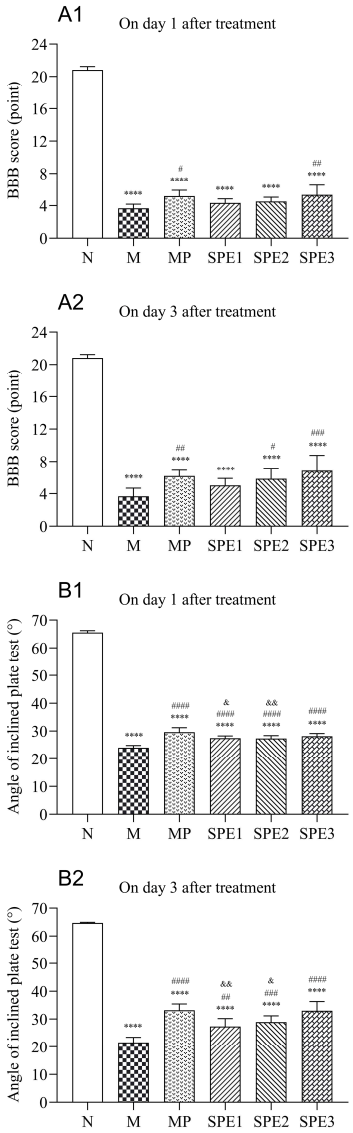

Fig. 4: Comparison of BBB scores and inclined plane test angles in each group rats after treatment ($\bar{x}$±s, n=6).
(A1) BBB scoring test on day 1 after treatment. (A2) BBB scoring test on day 3 after treatment. (B1) Inclined plane test on day 1 after treatment. (B2) Inclined plane test on day 3 after treatment. Compared with N group: $^{****}P$<0.0001; compared with M group: $^{\#}P$<0.05, $^{\#\#}P$<0.01, $^{\#\#\#}P$<0.001, $^{\#\#\#\#}P$<0.0001; compared with MP group: $^{\&}P$<0.05, $^{\&\&}P$<0.01.

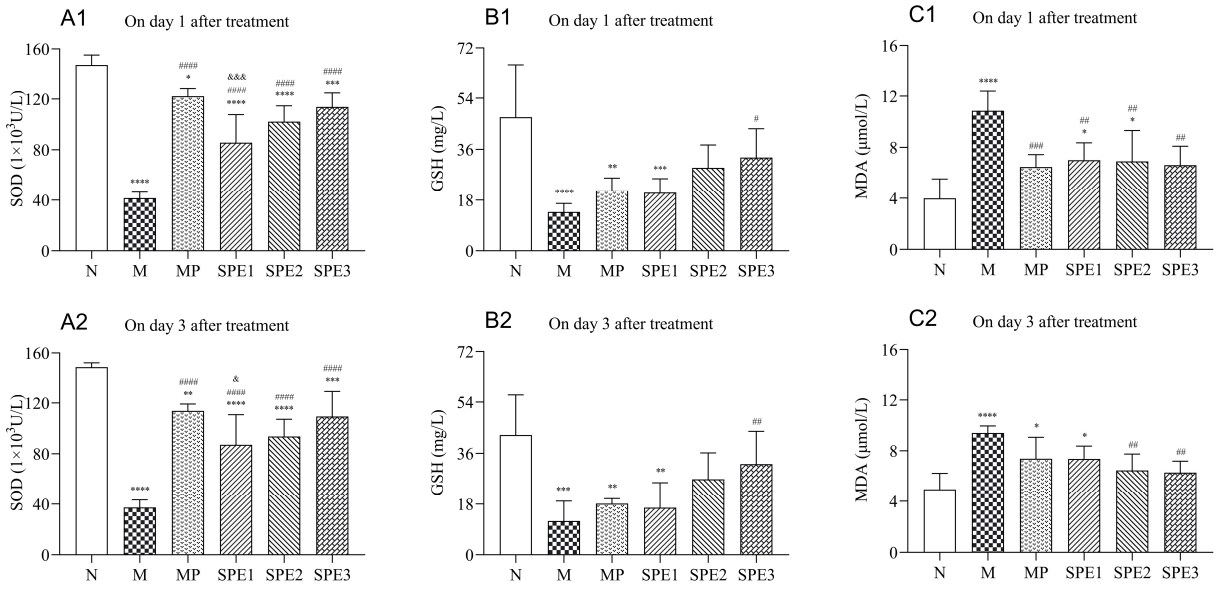

Fig. 5: Comparison of serum oxidative stress marker levels in each group rats after treatment ($\bar{x}\pm s$, n=6).

(A1) SOD on day 1 after treatment. (A2) SOD on day 3 after treatment. (B1) GSH on day 1 after treatment. (B2) GSH on day 3 after treatment. (C1) MDA on day 1 after treatment. (C2) MDA on day 3 after treatment. Compared with N group: $^{*}P$<0.05, $^{**}P$<0.01, $^{***}P$<0.001, $^{****}P$<0.0001; compared with M group: $^{\#}P$<0.05, $^{\#\#}P$<0.01, $^{\#\#\#}P$<0.001, $^{\#\#\#\#}P$<0.0001; compared with MP group: $^{\&}P$<0.05, $^{\&\&\&}P$<0.001.

These findings suggest that treatment with MP and SPE effectively decreased the serum levels of TNF-α, along with IL-1β, IL-6, IL-17 and IL-18. Furthermore, the efficacy of SPE was dose-dependent, with medium- and high-dose SPE exhibiting a level of inhibition of these inflammatory cytokines comparable to that observed in MP. Details are illustrated in fig. 6.

Effects of SPE on histopathological injury to the spinal cord in rats

On day 1 after treatment, no abnormal morphologic change or evidence of inflammatory reaction was observed in neurocytes in the spinal cord tissue of N group. In M group, multiple hemorrhagic areas with significant red blood cell infiltration (red arrow) were observed. In MP group, intensified cell staining, unclear nuclear-cytoplasmic boundaries, slight proliferation of glial cells and a few shrunken neuronal cells (grey arrow), along with occasional perivascular congestion (orange arrow) were observed. In SPE1 group, slight capillary congestion and dilation were observed (orange arrow), accompanied with mild bleeding in the central canal (red arrow). In SPE2 group, intensified cell staining, unclear nuclear-cytoplasmic boundaries (yellow arrow), a scarcity of shrunken neuronal cells and no significant glial cell proliferation were observed. In SPE3 group, the pathological features were similar to those observed in SPE2 group. Details are presented in fig. 7A.

On day 3 after treatment, nerve fibers remained intact with dense arrangement showing no evidence of neurocyte damage or glial cell proliferation in N group. In M group, intensified cell staining, perivascular congestion (orange arrow) and visible shrunken neuronal cells (grey arrow) were observed. In MP group, cell staining was also intensified, albeit with fewer shrunken neuronal cells (grey arrow). In SPE1 group, intensified cell staining, unclear nuclear-cytoplasmic boundaries (yellow arrow), a few shrunken neuronal cells (grey arrow) and occasional perivascular congestion (orange arrow) were observed. In SPE2 group, the staining and nuclear-cytoplasmic characteristics were comparable to those in SPE1 group, with sporadic perivascular congestion (orange arrow) and shrunken neuronal cells (grey arrow), along with no significant glial cell proliferation. In SPE3 group, a few shrunken neuronal cells were observed (grey arrow), with intensified cell staining, variable thickness of nerve fibers and no notable abnormalities identified. For further details, see fig. 7B.

DISCUSSION

The loss of motor function and subsequent recovery following ASCI are influenced not only by the primary damage inflicted by mechanical forces on the spinal cord tissue but also by secondary injuries resulting from post-injury pathophysiological changes, including hemorrhage, ischemia and hypoxia (Tsehay *et al*., 2022). Secondary spinal cord injuries can manifest within seconds of the initial injury and may persist for several weeks. These injuries primarily involve the immune, nervous and vascular systems, encompassing processes such as hemorrhage, ischemia, oxidative stress, inflammatory responses, neuronal cell death, demyelination and scar formation (Hu *et al*., 2023). The progressive and destructive nature of these secondary injuries often

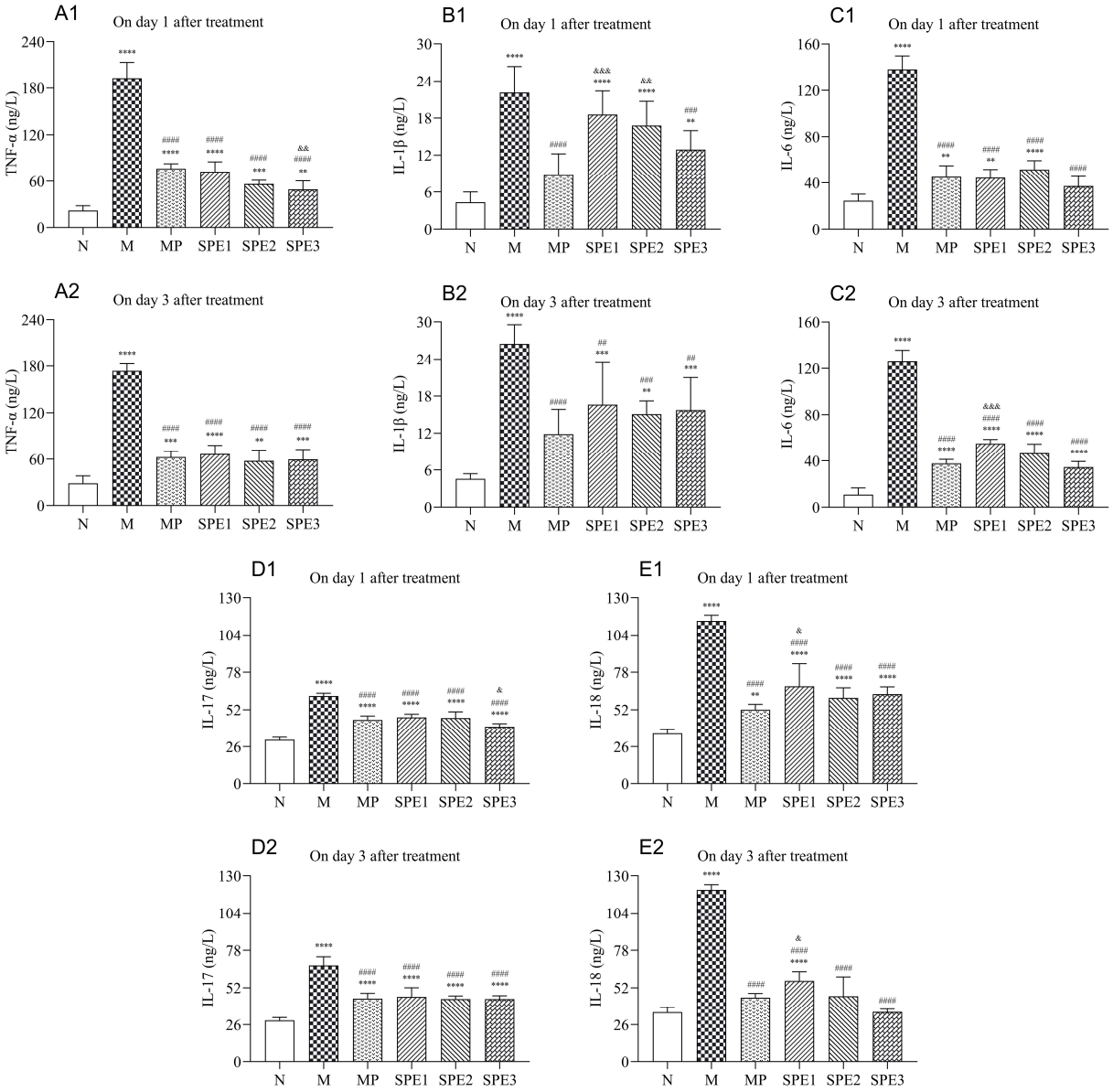

Fig. 6: Comparison of serum inflammatory cytokine levels in each group rats after treatment ($\bar{x}\pm s$, n=6).
(A1) TNF-α on day 1 after treatment. (A2) TNF-α on day 3 after treatment. (B1) IL-1β on day 1 after treatment. (B2) IL-1β on day 3 after treatment. (C1) IL-6 on day 1 after treatment. (C2) IL-6 on day 3 after treatment. (D1) IL-17 on day 1 after treatment. (D2) IL-17 on day 3 after treatment. (E1) IL-18 on day 1 after treatment. (E2) IL-18 on day 3 after treatment. Compared with N group: $^{**}P$<0.01, $^{***}P$<0.001, $^{****}P$<0.0001; compared with M group: $^{\#\#}P$<0.01, $^{\#\#\#}P$<0.001, $^{\#\#\#\#}P$<0.0001; compared with MP group: $^{\&}P$<0.05, $^{\&\&}P$<0.01, $^{\&\&\&}P$<0.001.

surpasses the extent of the primary damage (Rath and Balain, 2017; Lv *et al*., 2020). Therefore, effective clinical treatment of spinal cord injuries should prioritize strategies aimed at mitigating secondary damage to the spinal cord, thereby reducing mortality and disability rates while promoting functional recovery (Al-Nashash and All, 2022).

Methylprednisolone, commonly referred to as a corticosteroid, has traditionally been regarded as the first-line pharmacological agent for addressing ASCI due to its anti-inflammatory and neuroprotective properties (Sunshine *et al*., 2017). However, recent evidence from clinical studies has revealed substantial Level I evidence indicating serious complications associated with methylprednisolone pulse therapy, alongside a lack of definitive evidence supporting its efficacy in fundamentally improving the neurological prognosis of affected patients. Consequently, guidelines from reputable organizations, such as the American Association of Neurological Surgeons (AANS), have revised their recommendations regarding steroid usage from "recommended" to "not recommended" (Joaquim *et al*., 2020). This underscores the urgent need for the

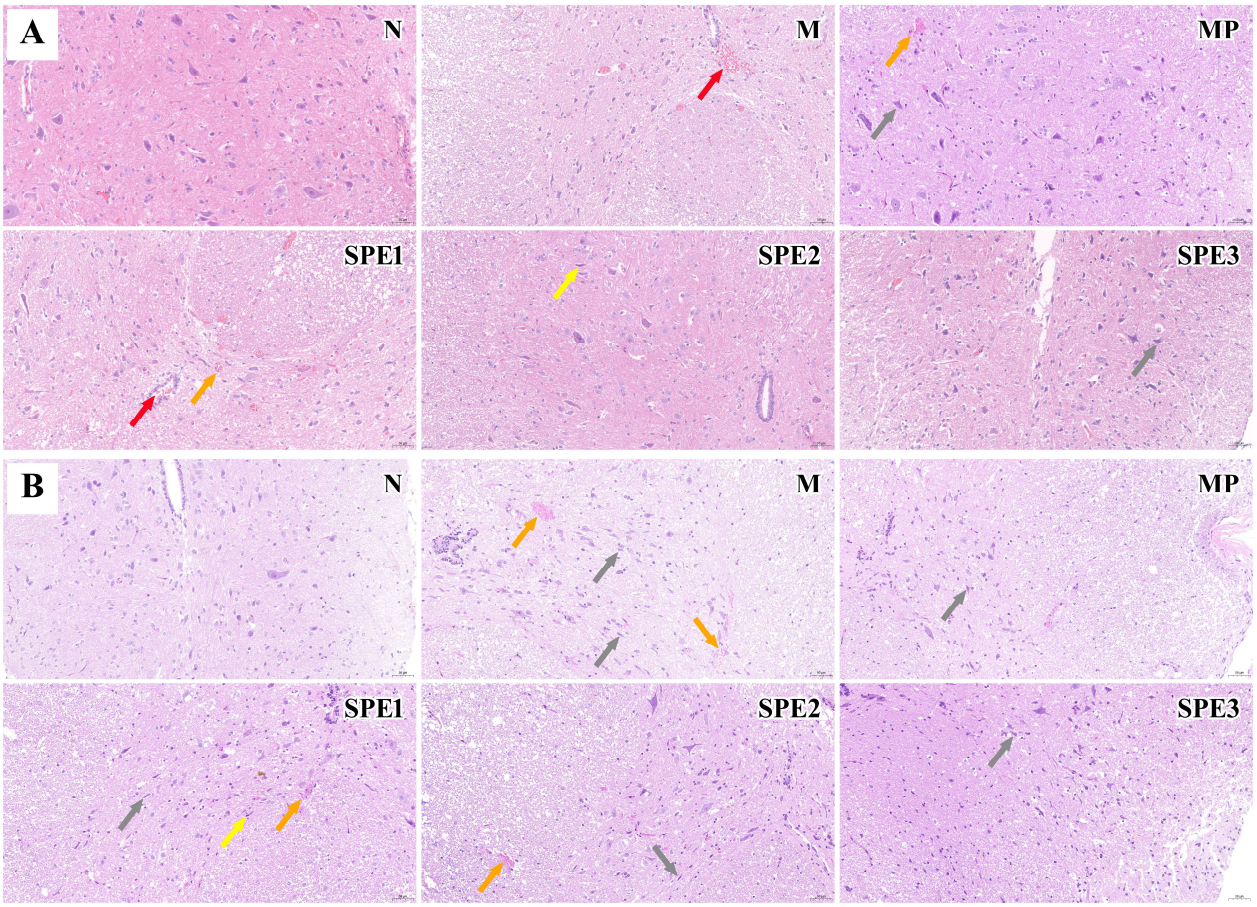

Fig. 7: Comparison of spinal cord histopathology in each group rats (H&E staining, 200×).

(A) On day 1 after treatment. (B) On day 3 after treatment. Red arrows: hemorrhage; orange arrows: perivascular congestion; yellow arrows: unclear boundary between nucleus and cytoplasm; grey arrows: shrunken neurons.

development of alternative pharmacological interventions aimed at the early treatment of ASCI to mitigate secondary damage. Growing evidence indicates that some traditional Chinese medicines exhibit promising therapeutic effects in alleviating ASCI-associated inflammatory damage.

The roots and rhizomes of *S. przewalskii* have long been used as traditional medicinal resources in China, knowing that they can balance menstrual cycles, enhance circulation, relieve stagnation and reduce discomfort (Editorial Committee of Chinese Academy of Sciences, 1977; Nanjing University of Chinese Medicine, 2006). The primary roots of *S. przewalskii* are characterized by their thickness and robustness, exhibiting a high concentration of active constituents, abundant availability and superior quality (Chu *et al*., 2003). *S. przewalskii* exhibits a range of pharmacological effects, including antioxidant (Matkowski *et al*., 2008), anti-inflammatory (Cheng and Yang, 2003) and anti-thrombotic activities (Lin *et al*., 2006). SPE developed by our research group predominantly contains phenolic acid compounds, notably rosmarinic acid and salvianolic acid B, characterized by a well-defined constituent and controllable quality (Zhu *et al*., 2016; Yang *et al*., 2017). Both rosmarinic acid and salvianolic acid B possess multiple phenolic hydroxyl groups, functioning as effective free radical scavengers and antioxidants (Zhao *et al*., 2008; Sánchez-Campillo *et al*., 2009) and demonstrating strong antioxidant and anti-inflammatory effects (Jiang *et al*., 2009; Lamien-Meda *et al*., 2010). The capacity of rosmarinic acid to scavenge free radicals is primarily attributed to its ortho-dihydroxy structure (Wang *et al*., 2019). Rosmarinic acid has been shown to significantly reduce oxidative stress in Wistar rats following spinal cord injury, demonstrating notable neuroprotective effects (Shang *et al*., 2017). The mainly constituent of the aqueous extract of *S. przewalskii*, magnesium lithospermate B (the magnesium salt of salvianolic acid B), exhibits robust antioxidative and free-radical scavenging properties (Zhang *et al*., 2004; Mehta *et al*., 2015) and demonstrates therapeutic potential against angina and cardiovascular damage (Wang *et al*., 2020).

Oxidative stress and inflammatory responses are the principal detrimental factors associated with ASCI (Fang *et al*., 2023). It is increasingly acknowledged that secondary injuries occurring after ASCI are closely linked

to cellular, molecular and biochemical changes in neurons, with significant consequences including the generation of free radicals and the oxidation of lipids and proteins (Alizadeh *et al*., 2019). The oxidative stress experiments conducted in our study demonstrated that SPE significantly increased serum levels of SOD and GSH in ASCI rats and markedly decreased the serum levels of MDA, thereby effectively inhibiting oxidative stress responses in these animals. Consistent with the findings reported in the literature, the oxidative stress experiments in this study showed that SPE could enhance BBB scores and inclined plane angles in ASCI rats, suggesting that its effects on motor function recovery and repair are primarily mediated by the synergistic actions of rosmarinic acid and salvianolic acid B, which serve as the key active components that elicit antioxidant stress responses.

Suppressing inflammation has emerged as one of the foremost strategies for mitigating the sequelae associated with ASCI (Allison and Ditor, 2015). Neuroinflammation plays a critical role in the pathogenesis of spinal cord injury, as the inflammatory response triggered by the injury can activate the NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome (Hung *et al*., 2020). Activation of the NLRP3 inflammasome facilitates the conversion of Pro-IL-1β and Pro-IL-18 into their mature forms, IL-1β and IL-18, through the activation of caspase-1 (Singh, 2022; Xu and Núñez, 2023). IL-1 induces secondary inflammation following spinal cord injury within 12 h. (Zong *et al*, 2012). Microglial cells serve as the primary inflammatory effector cells in the spinal cord and are critical regulatory factors in secondary spinal cord injury, readily activated by various stimuli post-injury. Following spinal cord injury, resting microglial cells can polarize into M1-type microglial cells, which recognize harmful stimuli and generate inflammatory cytokines, such as IL-1β, along with IL-6 and TNF-α (Tang and Le, 2016). Consequently, inhibiting the NLRP3/caspase-1/IL-1β or /IL-18 signaling pathways can effectively reduce tissue inflammation following spinal cord injury and facilitate the restoration of motor function (Sun *et al*., 2023). Additionally, research has demonstrated that IL-1β enhances the differentiation of T helper 17 (Th17) cells to produce IL-17 (Xiao *et al*., 2018). IL-17 is a critical proinflammatory cytokine, predominantly generated by Th17 cells, which plays a pivotal role in inflammatory processes (Korn *et al*., 2009).

Current literature emphasizes the significant involvement of IL-17 in the pathophysiology of spinal cord injury. Targeted interventions aimed at IL-17 or its downstream signaling pathways can effectively reduce secondary inflammatory responses after spinal cord injury, safeguard neuronal integrity and facilitate recovery. Within the first 12 h post-injury, IL-17 protein expression levels were markedly elevated and the presence of IL-17 stimulated the secretion of additional proinflammatory cytokines, including IL-6 and TNF-α, thereby intensifying inflammatory responses and exacerbating neuronal damage (Zong *et al*., 2014). Consequently, lowering IL-17 expression can diminish local inflammatory responses following spinal cord injury and enhance neuronal survival and functionality.

Previous studies, along with the results of this experiment, all showed a marked elevation in serum levels of inflammatory cytokines TNF-α, as well as IL-1β, IL-6, IL-17 and IL-18 in rats with spinal cord injury, indicating that such injuries induce robust inflammatory responses leading to severe secondary damage. It was found in our study that treatment with SPE in ASCI rats markedly reduced the serum levels of TNF-α, IL-1β, IL-6, IL-17 and IL-18, suggesting that SPE could inhibit the systemic inflammatory responses and improve the inflammatory environment in these rats. Previous investigations showed that rosmarinic acid exhibited substantial anti-inflammatory effects and was able to reduce the levels of IL-1β and TNF-α (Sherratt *et al*., 2019), suggesting that the action mechanism of SPE may encompass the inhibition of NLRP3 inflammasome activation and the modulation of microglial polarization, thereby mitigating the neuroinflammatory response elicited by spinal cord injury, decreasing the production of inflammatory cytokines, restoring the post-injury microenvironment and facilitating the recovery of motor function following spinal cord injury.

Research has demonstrated that rosmarinic acid can markedly mitigate hydrogen peroxide-induced cellular damage through its antioxidant and anti-apoptotic properties, thereby enhancing cellular viability (Gao *et al*., 2005). It can counteract apoptosis by enhancing the mitochondrial membrane potential and inhibiting the caspase-3 activity, curtail glial cell formation and protect against glutamate-induced apoptosis following central nervous system injury (Feng *et al*., 2019). In the current study, we observed multiple hemorrhagic areas, minor neuronal shrinkage and mild perivascular congestion within the spinal cord tissue of ASCI rats and SPE treatment improved neuronal integrity, reduced hemorrhage and attenuated inflammatory responses in the spinal cord tissue, thus markedly improving the pathological features of spinal cord injury and facilitating post-injury recovery.

This study has its limitations. Further research is essential to elucidate the specific mechanisms by which SPE exerts its effects in the treatment of ASCI, knowing that a comprehensive understanding of these mechanisms is critical for clarifying the potential pathways through which SPE mediates its therapeutic actions. Additionally, further investigation into the interactions between SPE and various molecular targets is necessary to facilitate the

development of more effective treatment strategies for ASCI.

CONCLUSION

SPE significantly increased the serum levels of oxidative stress markers SOD and GSH and concurrently reduced the serum levels of MDA and inflammatory cytokines TNF-α, IL-1β, IL-6, IL-17 and IL-18. Additionally, SPE mitigated neuronal damage within spinal cord tissue by minimizing hemorrhage and preserving neuronal integrity, thereby facilitating the recovery of motor function in ASCI rats. These results highlight the therapeutic potential of SPE in the management of ASCI.

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Authors' contributions
Ying Zhang: Performed experiments and wrote the original draft. Ying Guo: Performed experiments and revised the manuscript. Xun Tong and Zhonghai Zhou: Conducted the literature review and oversaw the study. Qian Hong, Bin Zhu, Lulu Wang, Hui Feng, and Liaoxin Fang: Collected and analyzed the data. Yang Yang: Conceived the study, designed the experiments, performed funding acquisition and critical revision, and approved the final version to be published. All authors have read and approved the final manuscript.

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Data availability statement
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical approval
All animal experimental protocols were approved by the ethics committee of the Affiliated Huaihai Hospital of Xuzhou Medical University, with animal welfare ethics approval number LL-2022DW04.

Conflict of interest
The authors declare that there are no conflicts of interest.

Supplementary data
https://www.pjps.pk/uploads/2025/11/SUP1762410384.pdf

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