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# Resveratrol Attenuates Cognitive Deficits of Traumatic Brain Injury by Activating p38 Signaling in the Brain

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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**Background:** Traumatic brain injury (TBI) is characterized by cognitive deficits, which was associated with brain oxidative stress and apoptosis. Resveratrol (RSV) is an anti-apoptotic and anti-oxidative. This study aimed to investigate neuroprotective effects and involved molecular mechanisms in TBI.

**Material/Methods:** RSV and p38 inhibitor were administrated to TBI rats. Cognitive deficits were evaluated by Morris water maze assay. Reactive oxygen species (ROS) and apoptosis were detected in rat brains by fluorescent staining. Western blotting was used to assess the phosphorylation of p38 and the expression levels of Nrf2, HO1, and activated caspase-3.

**Results:** RSV administration attenuated cognitive deficits of TBI rats. The ROS generation and apoptosis in the brain of TBI rats were suppressed by RSV treatment. Moreover, RSV treatment recovered activation of p38/Nrf2/HO1 signaling pathway. The co-administration of p38 inhibitor impaired RSV's attenuating effects on cognitive deficits, brain apoptosis, and ROS generation.

**Conclusions:** RSV attenuated cognitive deficits of TBI by inhibiting oxidative stress-mediated apoptosis via targeting p38/Nrf2 signaling.

**MeSH Keywords:** Apoptosis • Brain Injuries • Cognitive Dissonance • Oxidative Stress

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## Background

Traumatic brain injury (TBI) is recognized as alteration of brain pathology and/or function caused by external mechanical force [1]. TBI is one of the leading causes of morbidity and mortality resulting from neurological disorders around the world [2]. TBI is characterized by acute and chronic neurodegeneration and long-term cognitive deficits [3]. Though the mechanisms of TBI are still unclear, several previous investigations suggest the involvement of oxidative stress and apoptosis in TBI [4,5]. It has been well-established that oxidative stress induces cell apoptosis via multiple pathways such as death receptor, mitochondrial pathway, and endoplasmic reticulum stress signaling [6,7].

Increased harmful oxygen radicals have been identified in the brain several minutes after induction of TBI [8]. Elevated concentration of reactive oxygen species (ROS) have been found in brain tissue and cerebral spinal fluid from both animals and human patients with TBI [9]. p38 is a critical member of mitogen-activated protein kinases (MAPKs), playing a role in inducing the activation of antioxidant response element (ARE) which is a component of intracellular antioxidant defense system [10]. The activation of ARE signaling, further triggers the expressions and synthesis of the downstream anti-oxidant enzymes such as heme oxygenase (HO1) [11]. The activation of p38/Nrf2 signaling could increase the anti-oxidant potential which suppresses the apoptosis and inflammation responses [11].

In recent decades, nutritional supplementation has been recognized as a novel therapeutic strategy in treating chronic nervous system diseases. Natural products are optimal candidates for nutritional supplementation due to their effectiveness and biosafety. Resveratrol (RSV) is one of the bioactive natural polyphenolic compounds extracted from many fruits such as grapes and berries [12]. Previous studies have indicated a wide spectrum of bioactivities of RSV, including antioxidative, anti-apoptotic, anti-inflammatory, and neuroprotective activities [13]. For instance, RSV was proven to attenuates neuronal apoptosis and to reduce levels of inflammatory factors such as interleukin (IL)1β, IL10, and tumor necrosis factor (TNF)α in spinal cord injury. As a result, studies found that the neural function of the spinal cord was recovered with RSV treatment [14]. Importantly, RSV was found as a mediator regulating the activation of p38 MAPK signaling [15]. In this study, we hypothesized that RSV could exert neuroprotective effects against TBI by activating p38. A p38 inhibitor was also used to test our hypothesis. Our results add more evidence for RSV as an ideal therapeutic agent for TBI.

## Material and Methods

### Animals and establishment of TBI model

Sprague-Dawley (SD) rats (8-weeks old, male: female=1: 1, weighing 200–250 g) were provided by Animal Experimental Center of Hangzhou Normal University. Animals were kept in independent cages with free access to distilled water and standard chow. An artificial environment with appropriate temperature, humidity, and a 12-hour dark/light cycle was provided. All animal experimental protocols were approved by the Ethics Committee of Medical School of Hangzhou Normal University. The specific experimental procedures were carried out in accordance with Recommended Guideline for the Care and Use of Laboratory Animals issued by Chinese Council on Animal Research.

The TBI procedure was performed according to previous descriptions [16]. Briefly, SD rats were anesthetized by isoflurane inhalation. A heating pad was used to maintain the body temperature during the procedure. The skull was exposed by an incision and the impactor tip (Benchmark Stereotaxic Impactor, Leica Micro Systems) was placed sagittally between the bregma and lambda sutures. By using the pneumatic cylinder, the impact was delivered to the skull at velocity of 4 m/s and depth of 2 mm with a dwell time of 100 ms. Then the skin was closed, and the rats were placed in the resuscitation cage. RSV was dissolved in ethanol and diluted with distilled water with final concentrations at 0.2% (v/v). RSV resolution at concentrations of 0 mg/kg, 0.05 mg/kg and 0.1 mg/kg and were administrated to animals via oral gavage for 10 consecutive days, 7 days after the TBI procedure. Several rats were simultaneously treated with intraperitoneal injections of specific inhibitor of p38 MAPK inhibitor SB203580 (1 mg/kg per day, Selleck Chemicals). Rats were sacrificed by $CO_2$ suffocation. The brains were removed, and the right hemispheres were collected immediately and stored in 30% sucrose solution at 4°C for further experiments.

### ROS detection

The ROS indicator DHE (Beyotime) staining was used to detect the ROS generation *in situ*. Harvested brain tissue was immersed in optimal cutting temperature compound (Sakura) and cut into 10 μm sections. DHE was used to incubate the slides at final concentration of 10 μmol/L at 37°C in a humidified chamber for 45 minutes in the dark according to the instruction provided by the manufacturer. The ROS generation was detected with an inverted fluorescence microscope.

### Apoptosis assessment

The apoptotic cells were labeled by terminal transferase UTP nick end labeling assay (TUNEL). Brain tissue was cut into





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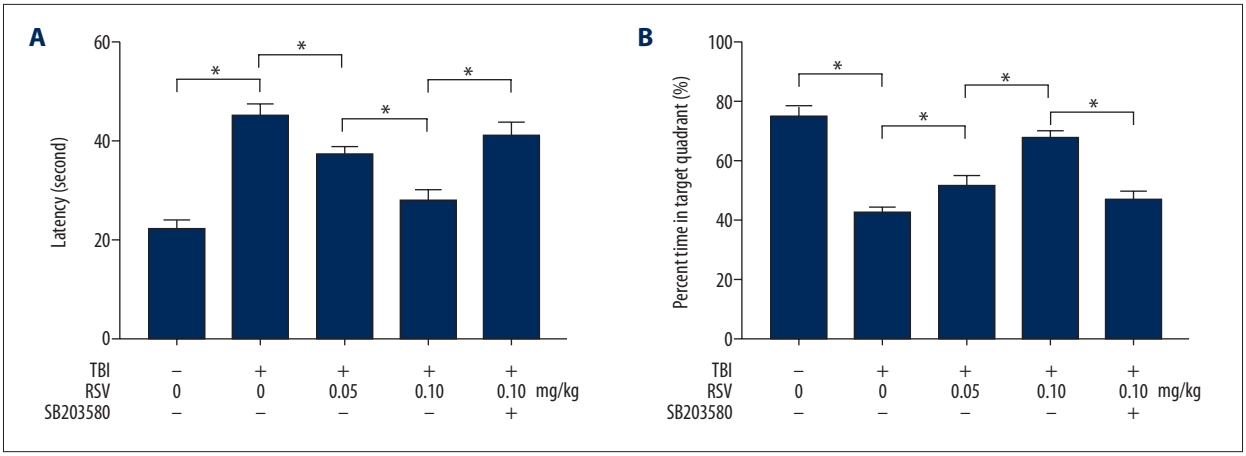


**Figure 1.** (**A**) Columns indicate the latency of TBI rats that received treatment with RSV and co-administration of p38 inhibitor SB203580. (**B**) Columns indicate the percent time in target quadrant of TBI rats that received treatment with RSV and co-administration of p38 inhibitor SB203580. (* *P*<0.05).

5-μm thick sections and treated with 20 μmol/L proteinase K (Sigma-Aldrich). Then the apoptosis was detected by using a TUNEL kit (Roche) in accordance with the manufacturer's instructions. The fluorescent images were then captured with an inverted fluorescence microscope.

### Total antioxidant capacity (TAC) evaluation

Harvested brain tissue was homogenized and centrifugated at 4°C at 12 000g for 5 minutes. The resulted supernatant was subjected to TAC determination with a T-AOC assay kit (Beytome) according to the protocol provided by the manufacturer. A plate reader (Bio-Rad) was used to detect the absorbance at 734 nm.

### Western blotting

Brain tissue was minced on ice in lysis buffer and the protein was isolated with Protein Extraction Kit (Beyotime). The nuclear protein was extracted with Nuclear Protein Extraction Kit (Beyotime). Protein samples were loaded and subjected to SDS-PAGE. The separated protein was then transferred to PVDF membranes electronically. After incubating with block buffer (Santa Cruz), the primary antibodies against p38 (1: 2500, Cell Signaling Tech), phospho-p38 (1: 2500, Cell Signaling Tech), Nrf2 (1: 5000, Abcam), HO1 (1: 5000, Abcam), β-actin (1: 5000, Abcam), and histone H3 (1: 5000, Abcam) were used to incubate the membranes at 4°C for 12 hours. After washing with TBST, secondary antibodies were used to incubate the membranes at room temperature for 2 hours. The immunoblots were visualized by using Western Blotting Luminal Reagent (Santa Cruz) and further analyzed with software ImageJ.

### Morris water maze (MWM)

In this study, the cognitive function was assessed by Morris water maze (MWM). Animals were trained for 3 days in a 50-cm height and 150-cm diameter Morris water maze (ACT-200A, Coulbourn) according to previous descriptions [17]. The tank was divided into 4 quadrants and filled with water at 20°C. A 10-cm diameter platform was hidden 2 cm beneath the water. Animals were allowed to adapt to the maze without the platform for 1 minute, for 3 days. After that, the animals were trained to locate the submerged platform depending on visual cues. A tracking system was used to record the time to reach the platform, which is recognized as latency. The percent time in a target quadrant was also recorded. Four independent trails were carried out from 4 starting points, randomly. All MWM assays were carried out at a specific time during the day to eliminate the time-associated variations.

### Statistics

The data acquired in this study was put in Excel (Microsoft) and further analyzed by SPSS (ver. 16.0, SPSS). Differences between groups were analyzed by Student's *t*-tests and one-way ANOVA. SNK tests were used as post-hot test. When $P<0.05$, the difference was considered statistically significant.

## Results

### RSV attenuated cognitive dysfunction in TBI rats which was impaired by p38 inhibitor

As demonstrated in Figure1, the latency was increased while the percent time in a target quadrant was significantly decreased in the TBI rats compared with the normal control





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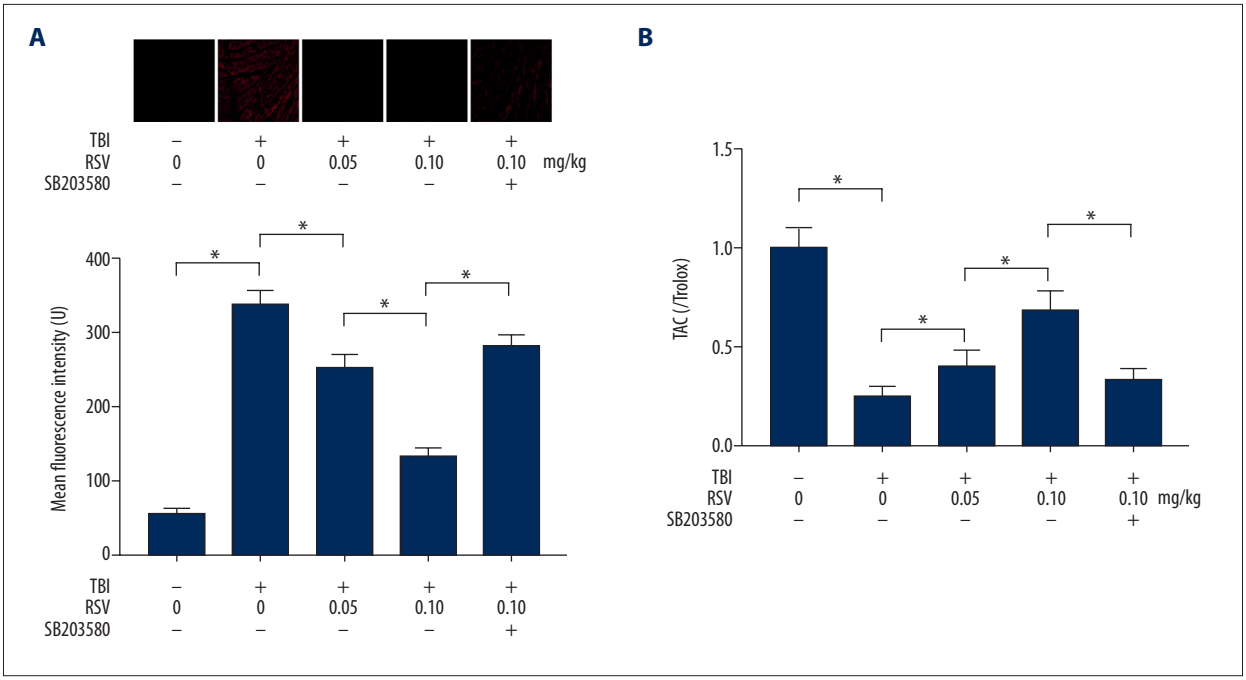


**Figure 2.** (**A**) The upper panel indicates the captured fluorescent images of DHE staining of brain tissue. Columns on the lower panel indicate the detected mean fluorescent intensities of DHE staining of brain tissue from TBI rats that received treatment with RSV and co-administration of p38 inhibitor SB203580. (**B**) Columns indicate the TAC of brain tissue from TBI rats that received treatment with RSV and co-administration of p38 inhibitor SB203580. (* *P*<0.05).

rats. The latency and percent time in a target quadrant were used to indicate the spatial memory and reference memory respectively. Treatment with RSV dramatically increased latency and decreased percent time in the target quadrant for the TBI rats. The co-administration of SB203580 impaired the therapeutic effects of RSV on cognitive dysfunction in the TBI rats.

### RSV reduced ROS generation and increased TAC in the brains of the TBI rats which were impaired by p38 inhibitor

The ROS detected by DHE are shown in Figure 2. In this study, TAC was employed to measure the combined non-enzymatic antioxidant capacity of biological samples, providing an overall capability to counteract the oxidative stress. The ROS production increased, and TAC decreased significantly in the brain tissue compared with the normal control tissue. The RSV administration decreased the ROS production and increased TAC in brain tissue in a dosage-dependent manner. However, the co-administration of SB203580 impaired the anti-oxidant effect of RSV.

### RSV suppressed apoptosis in the brain of TBI rats which was impaired by p38 inhibitor

The results of the TUNEL assay are shown in Figure 3. The administration of RSV significantly attenuated the apoptosis in

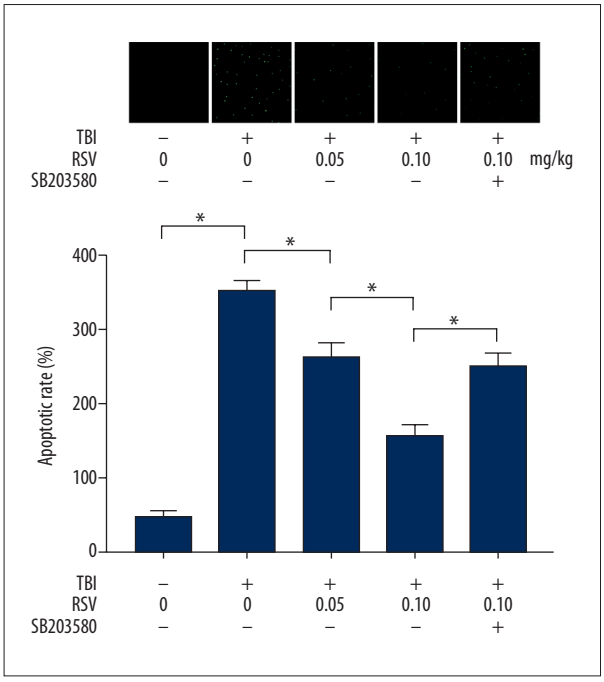


**Figure 3.** (**A**) The captured fluorescent images of TUNEL assay of brain tissue are shown. The apoptotic cells were positively stained. (**B**) Columns indicate the apoptotic rate in brain sections from TBI rats that received treatment with RSV and co-administration of p38 inhibitor SB203580. (* *P*<0.05).





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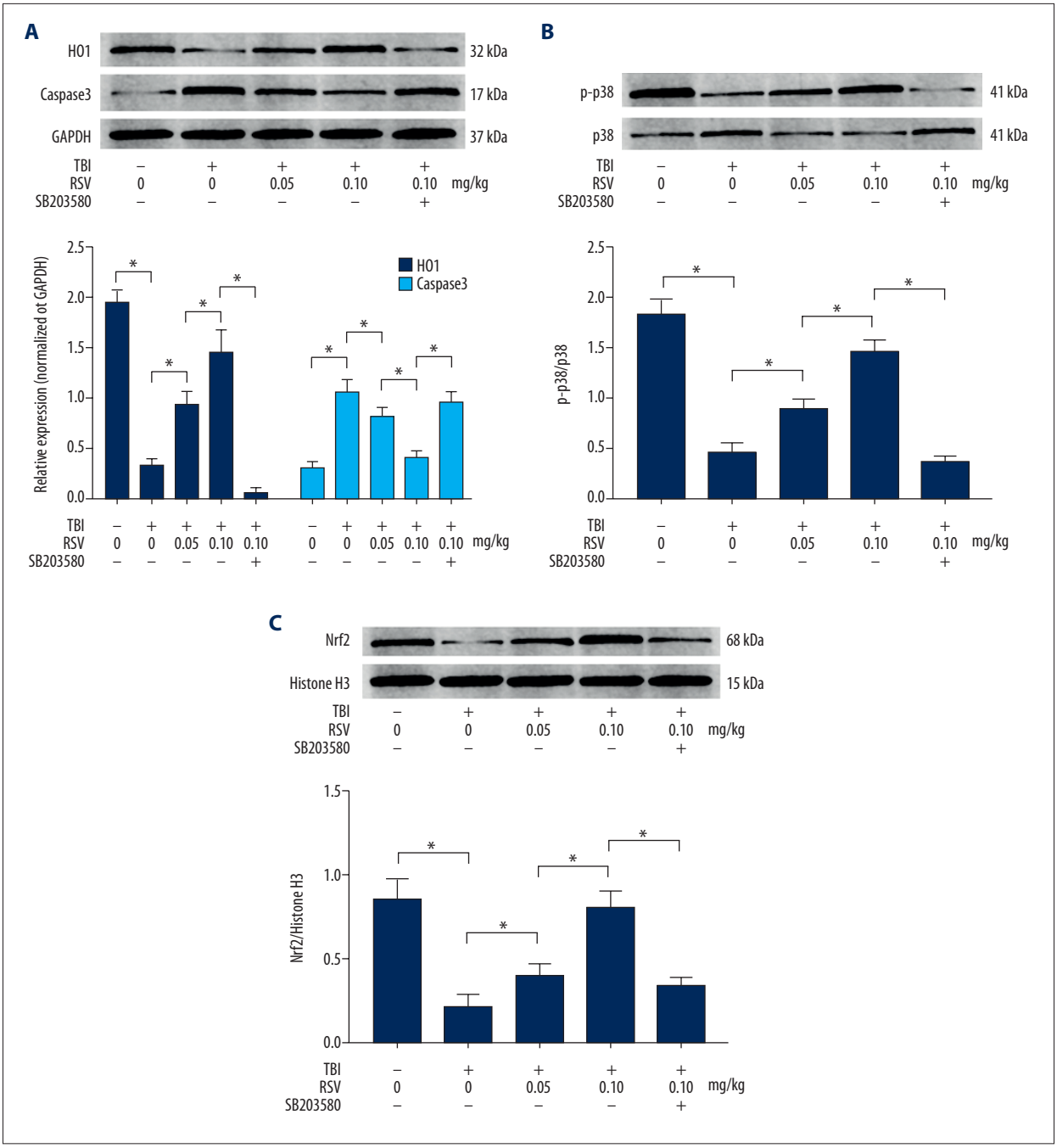


**Figure 4.** (**A**) The upper panel demonstrates the immunoblots of HO1, caspase-3, and their internal reference GAPDH in brain tissue. Columns on the lower panel indicate the relative expression levels of HO1 and caspase-3 in brain from TBI rats that received treatment with RSV and co-administration of p38 inhibitor SB203580 respectively. (**B**) The upper panel demonstrates the immunoblots of p-p38 and p38 in brain tissue. Columns on the lower panel indicate the ratio of p-p38/p38 in brain from TBI rats that received treatment with RSV and co-administration of p38 inhibitor SB203580. (**C**) The upper panel demonstrates the immunoblots of Nrf2, its internal reference histone h3 in brain tissue. Columns on the lower panel indicate the ratio of Nrf2/histone h3 in the brain from TBI rats that received treatment with RSV and co-administration of p38 inhibitor SB203580. (* $P<0.05$).





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the brain of the TBI rats in a dosage-dependent manner. The co-administration of SB203580 impaired the anti-apoptotic effects of RSV in the brain of the TBI rats.

**RSV inhibited the activation p38/Nrf2 pathway in the brain of TBI rats but was impaired by p38 inhibitor**

The results are shown in Figure 4. The expression levels of Nrf2, HO1, as well as the phosphorylation level of p38 were decreased in the brain from the TBI rats. As an important intracellular transducer, p38 conducts anti-oxidant signaling which facilitates the nuclear translocation of the nuclear factor Nrf2. HO1 is a potent member of intracellular anti-oxidant system and its transcription would be promoted by Nrf2 nuclear translocation. Treatment with RSV increased the expression levels of Nrf2, HO1, and the phosphorylation level of p38 in the brain of TBI rats. However, the phosphorylation of p38 was blocked by SB203580 treatment, as a result, the expression levels of Nrf2 and HO1 were decreased in the brain from the RSV-treated TBI rats.

## Discussion

TBI is often a result of external mechanical forces caused by car accidents, violence, gunshots, combat injuries, or objects penetrating the skull. The brain function and physiology are temporarily or permanently impaired in TBI patients. TBI survivors exhibit many clinical manifestations including various neurological disorders and disabilities which are recognized as chronic manifestations [18]. There are very few available agents that can effectively treat TBI. In recent decades, nutritional supplements from natural plants have attracted researcher's attention because of their various biological activities, effectiveness, and biosafety. In the present study, a TBI animal model was established, which received RSV administration. The therapeutic effect of RSV on TBI was investigated. Moreover, the possibly involved molecular mechanism was also studied.

TBI process includes the development of neurodegeneration which could chronically impair brain function causing cognitive dysfunctions [2]. Difficulties in concentration, attention and memory, changes in balance and vision, spontaneous seizures, and sleep disturbance are the typical clinical manifestations of cognitive disorders [19]. In this study, MWM was used to assess the cognitive dysfunctions of TBI rats. The results showed that both latency and percent time in the target quadrant were significantly altered in TBI rats. Specifically, the latency indicated the spatial memory, while the percent time in the target quadrant indicated the reference memory. These results suggested that the cognitive deficits were exacerbated in TBI animals.

Oxidative associated neuron apoptosis is believed to play critical roles in occurrence and development of cognitive deficits [20]. Previous studies have indicated the accumulation of ROS in the brain of several neurodegenerative diseases including Alzheimer disease, Parkinson disease and TBI [21]. The application of anti-oxidant agents attenuated the brain dysfunctions of these diseases [22]. Moreover, it was described that TBI-induced cognitive dysfunction was associated with the neuron loss in brain [23]. In the current study, we found that the ROS generation was elevated, and the apoptosis was increased in brain harvested from TBI rats. The oxidative status was maintained by the oxidant-antioxidant system and belongs to the "cap n collar" family of basic leucine zipper transcription factors; Nrf2 translocate to nuclei to take part in inducing expression of antioxidant enzymes such as HO1 by binding to ARE [24]. The activation of Nrf2/ARE was directed by its upstream kinases such as p38 [25]. The multifunction kinase p38 is inhibited by binding with Keap1 under normal physiological conditions. When encountering pathological challenges such as oxidative stress, the Keap1 would disassociate from p38 which was further activated by auto-phosphorylation [26]. In this study, we found that compared with normal control, the phosphorylation level of p38 was dramatically downregulated. As a result, the expression level of HO1 was reduced in TBI brains.

RSV, also referred to as 3,5,4'-trihydroxystilbene, is one of the natural phytoalexin extracted from some kinds of plant seeds such as grape seeds [27]. Many previous studies have suggested that RSV has the ability to interfere with the pathological processes in neurodegenerative diseases [28]. Multiple mechanisms have been proposed to interpret the neuroprotective effects of RSV, including the anti-oxidative and anti-apoptotic activities of RSV [29]. In this study, we found that the RSV administration relieved the cognitive deficits by recovering the spatial memory and reference memory. The ROS generation and apoptosis were dramatically attenuated by RSV administration. Moreover, RSV treatment also recovered the phosphorylation level of p38. As a result, the Nrf2 nuclear tranlocation and the HO1 expression were increased. These results indicated that p38 was the molecular target of RSV in attenuating cognitive deficits in TBI.

## Conclusions

In order to further test the molecular mechanism of RSV, p38 inhibitor SB203580 was co-administrated to the rats with RSV. SB203580 is a selective inhibitor of p38 which inhibits the p38 catalytic activity by binding to its ATP pocket [30]. The results showed that the co-administration of p38 inhibitor impaired the therapeutic effects of RSV on TBI. Specifically, the administration of SB203508 blocked the recovery of p38 phosphorylation





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by RSV. The subsequent nuclear translocation of Nrf2 and the expression of HO1 were also impaired in RSV-treated TBI rats. As a result, SB203508 suppressed the anti-oxidative and anti-apoptotic effects of RSV on TBI brains. Taken together, data collected in this study suggested that RSV attenuated cognitive deficits of TBI by suppressing oxidative stress-mediated apoptosis in the brain. p38/Nrf2 signaling was considered one of the molecular targets of RSV. We believe that our data would not only add more information on the pathogenesis of TBI, but also provide a theoretical basis for application of RSV in clinical treatment of TBI. However, there are also limitations to this study. According to previous reports, neural injuries, such as spinal cord injury and TBI, are the pathological factors activating p38 signaling. Our results also found activation of p38 following TBI. However, if a p38 activator was also employed, our conclusion would be more persuasive and solid.

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