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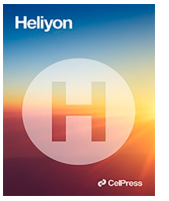

Research article

Ginkgolide A attenuated apoptosis via inhibition of oxidative stress in mice with traumatic brain injury

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ABSTRACT

Traumatic brain injury (TBI) is the main cause of death among young adults and the main cause of mortality and disability for all ages groups worldwide. Ginkgolides terpenoid compounds unique to Ginkgo biloba, which have protective effects on cardiovascular and cerebrovascular diseases. The aim of this study is to investigate whether ginkgolide A (GA) can improve TBI in mice and whether it can alleviate cell apoptosis in the brain of TBI mice by reducing oxidative stress. Mice received TBI and GA administration for 7 days. Neurological deficits were monitored and brain tissues were examined for molecular pathological markers. TBI mice had more severer neurobehavioral deficits compared with sham group, which could be improved by administration of GA. GA administration improveed Modified Neurological Severity Scale (mNSS) scores, Grid-Walking test and Rotarod test of TBI mice. The apoptosis increased in TBI mice, and reduced after GA treatment. The biomarkers of oxidative stress 8-OHdG and malondialdehyde (MDA) in the brain of TBI mice increased, while SOD reduced. These changes were reversed after GA administration. These outcomes showed that GA could raise neurobehavioral deficiency of TBI mice. GA treatment could attenuate apoptosis in TBI mice by reducing oxidative stress.

1. Introduction

Traumatic brain injury (TBI) is a disease with structural or physiological brain dysfunction caused by external forces, and is one of the main causes of death and disability around the world [1,2]. TBI is a common clinical emergency and serious public health problem [3] which is defined as alteration in brain function or other brain pathology caused by external forces. Therefore, it is crucial to find key molecules and drugs for TBI and explore their biological mechanisms.

Ginkgolides area unique terpenoid compound of *Ginkgo biloba*, which can be divided into ginkgolide A (GA), B, C, J, K, L and M based on their chemical structures [4]. A previous study verified [5] the protective effects of *Ginkgo biloba* extracts on cardiovascular diseases. It has been shown that Ginkgo biloba extracts (EGb 761) have neuroprotective effects in many pathological models [6]. Ginkgolide B (GB) improves hypoxic-ischemic brain injury in the neonatal rats [7]. GA and GB mediated neuroprotective effects on focal ischemic behavior [8]. Nevertheless, the pharmacological role of GA in alleviating brain dysfunction induced by TBI is still unclear.

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Cell death plays a crucial role in physiologic and pathophysiologic processes, and the pathogenesis of human diseases is closely related to this process [9,10]. Apoptosis is a kind of cell death, usually caused by some proapoptotic stimuli, such as endoplasmic reticulum stress and accumulation of reactive oxygen species [11]. Apoptosis played a significant role in central nervous system disorders, including TBI [12]. GA significantly inhibited neurotoxicity of sodium nitroprusside on human neuroblastoma cell line SK-N-SH induced by sodium nitroprusside (SNP) by blocking the inhibition of cell growth and apoptosis induced by SNP [13]. This study was to explore whether GA alleviated TBI by inhibiting cell apoptosis.

Oxidative stress is a component of many diseases, involving chemical reactions of so-called reactive species derived from oxygen and nitrogen [14]. Ginkgolides protect neurons from oxidative stress injury by enhancing the increases of antioxidant proteins [15]. GB and its extracts have extensive anti-inflammatory and antioxidant properties, which have beneficial effects on promoting and managing health [16]. The aim of this study was to investigate whether GA alleviated TBI by reducing oxidative stress.

In summary, the purpose of this research was to find the impacts of GA on TBI and investigate whether GA alleviated TBI by reducing oxidative stress and inhibiting cell apoptosis in brain.

2. Materials and methods

2.1. Animals

8–10 week old male C57BL6/J mice (Vital River Biological Co., Ltd, Beijing, China) were raised in a standard environment with a 12/12 light/dark cycle and were free access to food and water. Animal procedures were approved by the Experimental Animal Care and Use Committee ofXuzhou Medical University based on the Guide for the Care and Use of Laboratory Animals (NIH publication No. 85-23, 1996).

2.2. TBI mouse model and GA treatment

Induced TBI by a controlled cortical impact device (RWD Life Science, Shenzhen, China). Anesthetized the mice with isoflurane (1.5–2.5 %). Drilled a 5 mm diameter hole on the right cerebral hemisphere (2.0 mm posterior from bregma and 2.0 mm lateral to the sagittal suture) after retracting the scalp and fascia to expose the dura. Used a 3 mm-flat impactor tip to impact the exposed dual (impact parameters: velocity: 3.0 m/s, depth: 2 mm, dwell time: 100 ms). After the surgery, sutured the scalp incision, and placed the mice in a heating pad until anesthesia was restored. Sham-injured mice underwent all these procedures without any impact. Simultaneously, injected GA intraperitoneally once a day for 7 days (5 mg/kg; Sigma, MO, USA) [5], and physiological saline was used as the carrier. Lesion volume was assessed in accordance with previous reports [17,18].

2.3. Neurobehavioral function assessments

At the 0, 1, 3, and 7 days after TBI, a researcher who was not aware of the experimental design recorded neurobehavioral assessments with the modifed Neurological Severity Score (mNSS), Grid-Walking Test and Rotarod Test according to a previous report [2]. Briefly, rats underwent a 2-day testing phase with rotarod (IITC Life Science, CA, USA), which gradually accelerated from 5 to 45 rpm over 5 min. During the procedure, the latency to fall was recorded as the time before rats fell off the rod or gripped around for two successive revolutions at 0, 1, 3 and 7 after TBI. The mean latency was measured at different time points by investigators who were blinded to group information.

3. ELISA

Used enzyme immunoassay kit (USCN Life Science Inc., Wuhan, China) to detect MDA level in the brain of mice according to the manufacturer's instructions.

3.1. Superoxide dismutase (SOD) activity level

Seven days after GA administration, the mice were sacrificed under deep anesthesia. The brain tissue was quickly removed from the ice dish, and the damaged brain tissue was selected. Used a microplate reader (BioTek, VT, USA) to measure superoxide dismutase (SOD) according to the manufacturer's instructions (Beyotime Biotechnology, Shanghai, China).

3.2. Immunofluorescence

Fixed the brain samples with 4 % paraformaldehyde, embedded in paraffin, and cut into 5-μm-thick slides. Then, incubated the samples with primary antibody against Bax, CC3 (Abcam, Shanghai, China) and 8-hydroxy-2' -deoxyguanosine (8-OHdG; Santa, TX, USA) at 4 °C overnight. Then, incubated them with corresponding secondary antibodies (Jackson ImmunoResearch, PA, USA) at room temperature for 2 h. After that, performed nuclear cells re-staining with 4',6-diamidino-2-phenylindole (DAPI; Life Technologies Co., NY, USA). Captured the images with a fluorescence microscope (Carl Zeiss GmbH, Oberkochen, Germany). Five fields were randomly chosen from each section of the three to five consecutive brain sections from each rat.

3.3. Statistical analyses

Data was presented as mean ± standard error of the mean (SEM). Used GraphPad Prism 7.0 (GraphPad Software Inc., CA, USA) for statistical processing. Compared differences between groups and among multiple groups respectively with t-tests, one-way analysis of variance (ANOVA) and Bonferroni post tests. Two-tailed $P < 0.05$ was considered statistically significant.

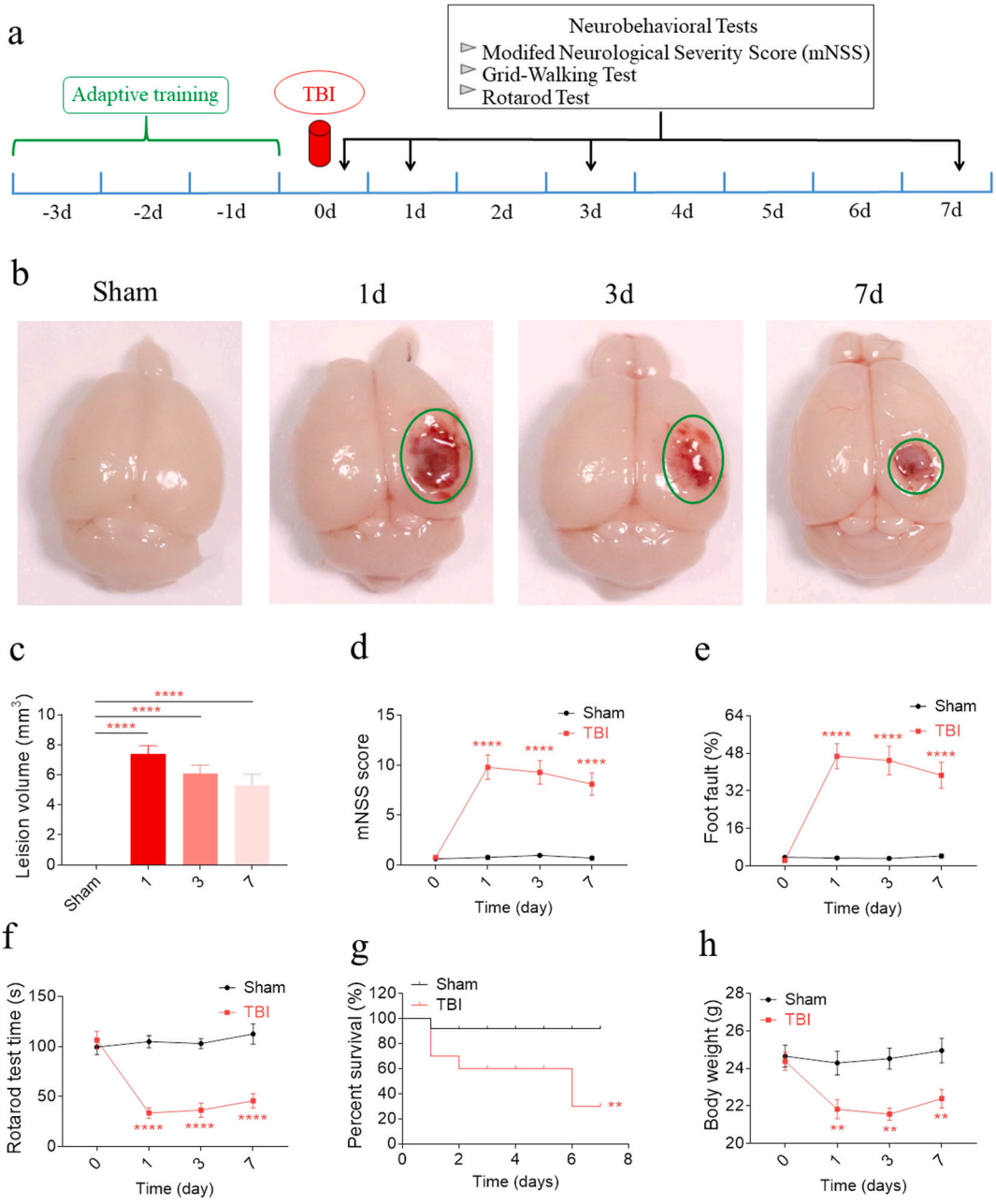

Fig. 1. Model of TBI. a, The experimental timeline. b, The whole brains sham and different TBI mice. c, The injury volume was increased in TBI mice. d, e and f, The neurobehavioral function was impaired in mice after TBI. g, The percent survival was lower in TBI mice. h, The body weight of mice was reduced in TBI group. Expressed the outcomes as mean ± SEM. n = 8 for each group. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ and ****$P <$ 0.0001 compared with Sham group.

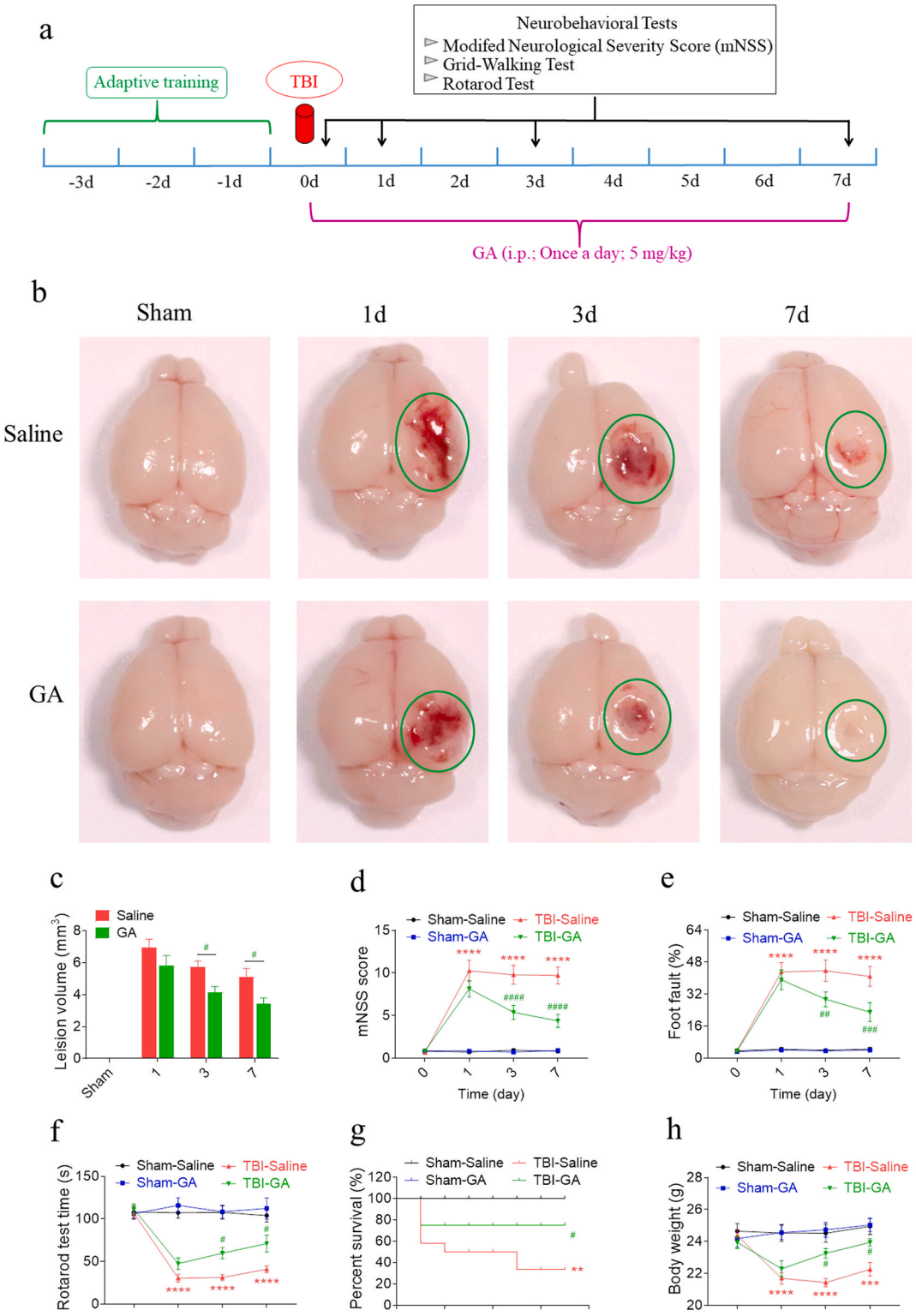

Fig. 2. GA alleviated motor function deficits of mice after TBI. a, The experimental timeline. b, GA administration alleviated extravasated blood in ipsilateral cortex of TBI mice. c, GA administration alleviated injury volume in ipsilateral cortex of TBI mice. d, e and f, GA administration alleviated neurobehavioral deficiency of TBI mice. g, GA administration alleviated the decrease of percent survival of TBI mice. h, GA administration alleviated the decrease of body weight of TBI mice. Expressed the outcomes as mean ± SEM. n = 8 for each group. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ and $^{****}P < 0.0001$ compared with Sham-Saline group. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ and $^{\#\#\#\#}P < 0.0001$ compared with TBI-Saline group.

4. Results

4.1. Model of TBI

The experimental timeline was shown in Fig. 1a. All mice used to evaluate neurobehavioral outcomes would undergo 3 days of adaptive training before TBI. Randomly divided the mice into Sham group and TBI group for subsequent experiments. The whole brains were shown in Fig. 1b, including the sham and different TBI groups (1 day, 3 days and 7 days after injury, respectively). The

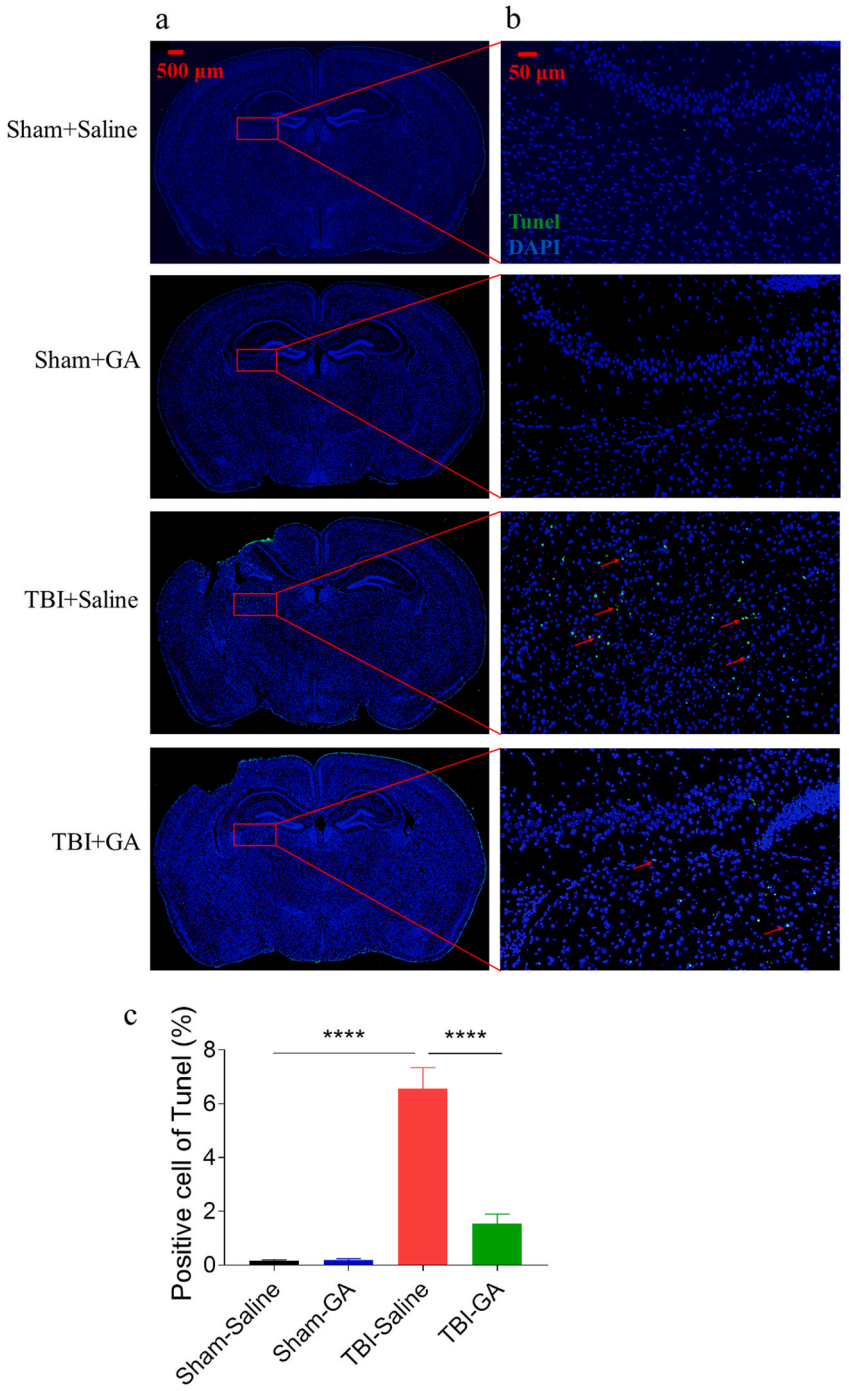

Fig. 3. GA attenuated tunel positive cell number in brain of mice after TBI. Tunel positive cell number raised in TBI mice, and was inhibited after administration of GA. Magnification 2.5× in a, and magnification 30× in b. n = 5 for each group.

injury volume was increased in TBI mice (Fig. 1c). Next, evaluated the neurobehavioral function of mice after TBI. TBI mice had more severer neurobehavioral deficiency compared with sham group, such as mNSS (Fig. 1d), Grid-Walking test (Fig. 1e), and Rotarod test (Fig. 1f). The survival rate of mice in the TBI group was significantly lower than that of the Sham group (Fig. 1g). The body weight of mice was reduced in TBI group (Fig. 1h).

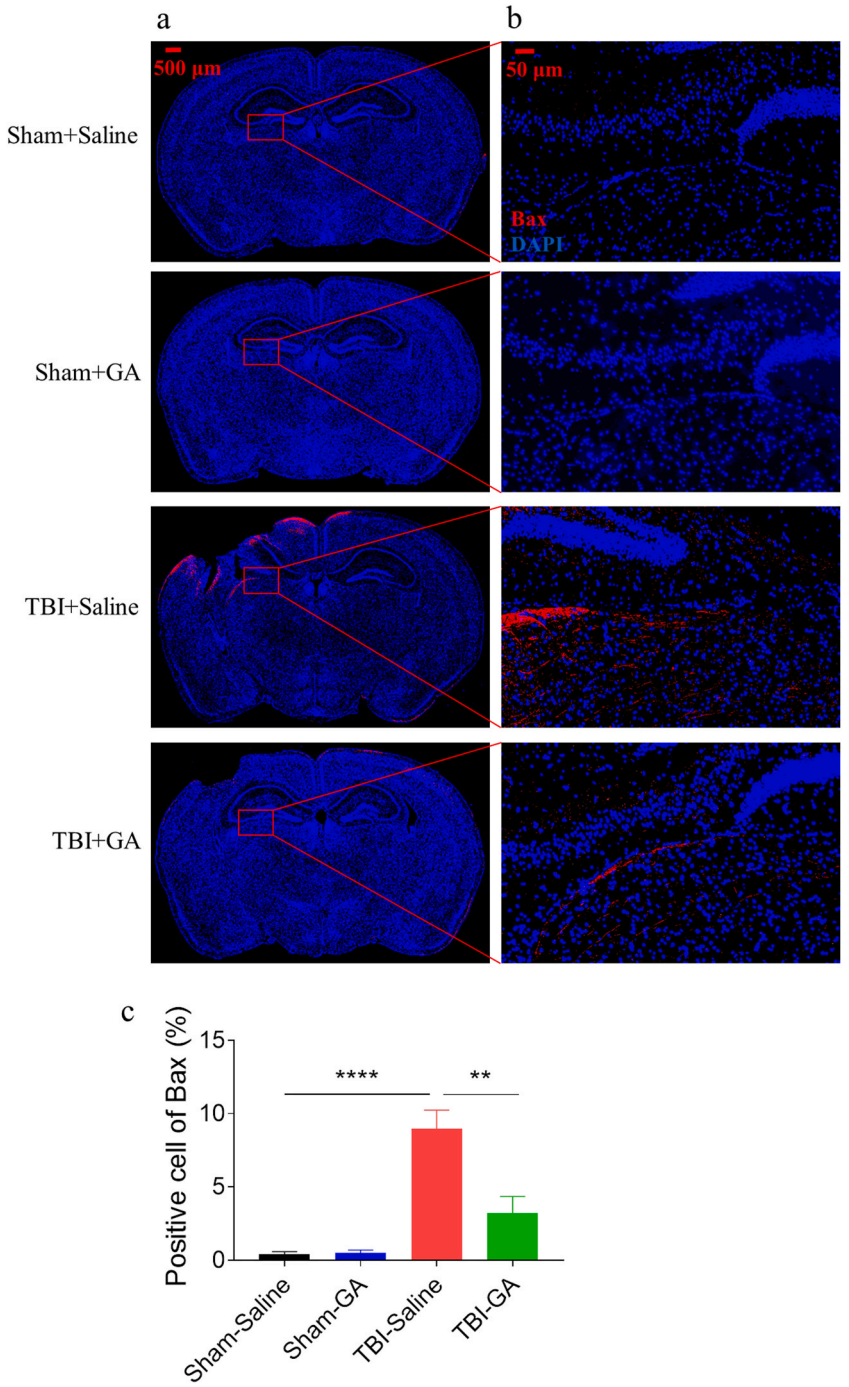

Fig. 4. GA attenuated bax positive cell number in brain of mice after TBI. Bax positive cell number raised in TBI mice, and was inhibited after administration of GA. Magnification 2.5× in a, and magnification 30× in b. n = 5 for each group.

4.2. GA alleviated motor function deficits in mice after TBI

The timeline of this part of experiments was shown as Fig. 2a. GA administration alleviated extravasated blood in ipsilateral cortex (Fig. 2b) and injury volume (Fig. 2c) of TBI mice. After GA treatment, evaluated neurobehavioral function recovery of TBI mice. TBI mice showed more severer neurobehavioral defects compared with sham group, which could be improved by administration of GA. On 3 and 7 days after TBI, GA administration showed improvements in mNSS scores (Fig. 2d), Grid-Walking test (Fig. 2e) and Rotarod test (Fig. 2f). The survival rate of mice in the TBI group was significantly lower than that of the Sham group, which was reversed after GA

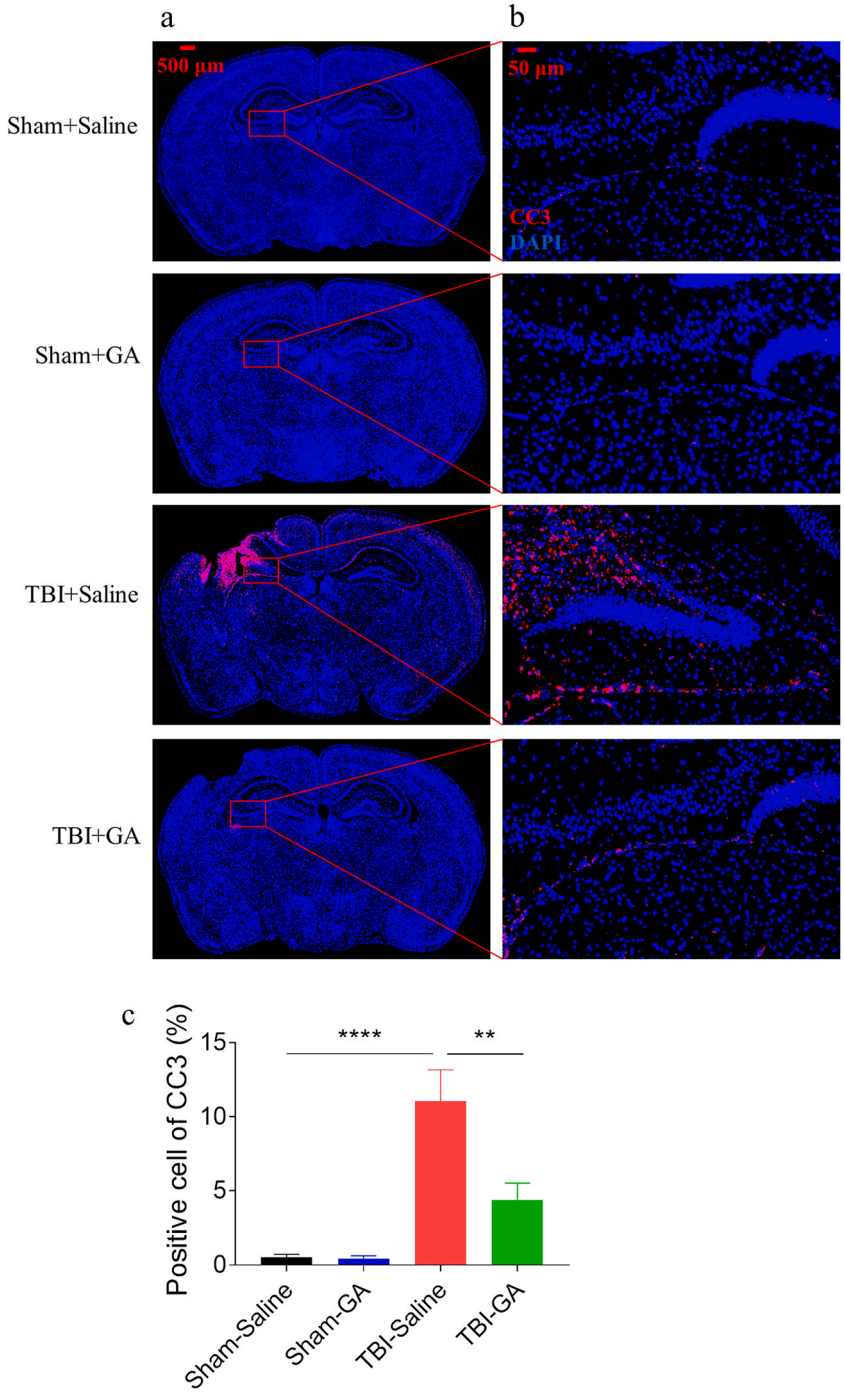

Fig. 5. GA attenuated CC3 positive cell number in brain of mice after TBI. CC3 positive cell number raised in TBI mice, and was inhibited after administration of GA. Magnification 2.5× in a, and magnification 30× in b. n = 5 for each group.

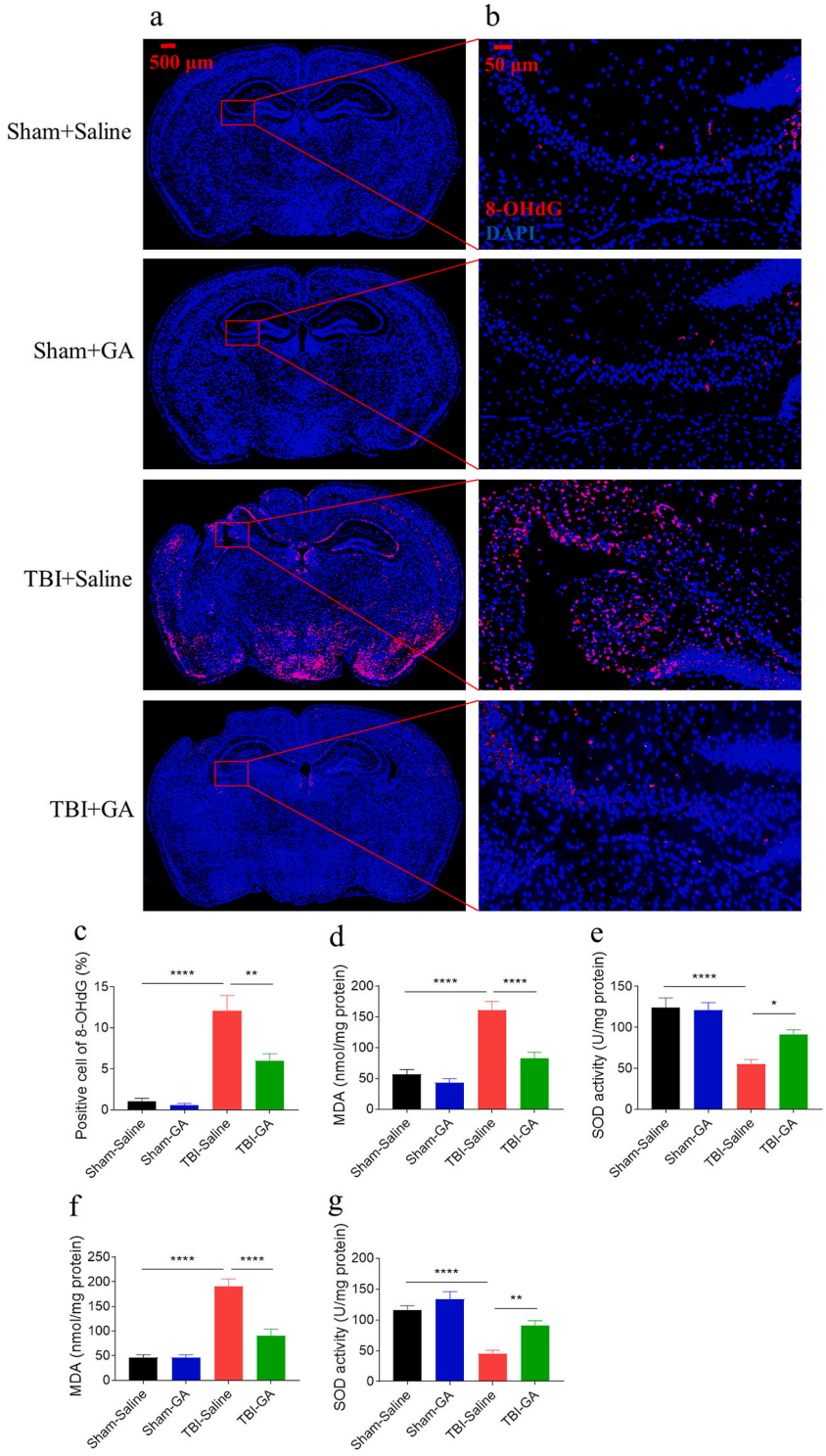

Fig. 6. GA attenuated oxidative stress in mice after TBI. a, b and c, GA administration inhibited the raise of 8-OHdG in TBI mice after 7 days. d, GA administration inhibited the raise of MDA in TBI mice after 7 days. e, GA administration reversed the decrease of SOD activity in TBI mice after 7 days. f, GA administration inhibited the raise of MDA in TBI mice after 3 days. g, GA administration reversed the decrease of SOD activity in TBI mice after 3 days. Magnification 2.5× in a, and magnification 30× in b. Expressed the outcomes as mean ± SEM. n = 5 (a and b) or 8 (c or d) for each group. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ and $^{****}P < 0.0001$.

administration (Fig. 2g). The decrease of body weight was also improved after administration of GA (Fig. 2h).

4.3. GA attenuated apoptosis in the brain of mice after TBI

Apoptosis was detected at 7 days after TBI. The result showed that tunel positive cell number raised in the brain of TBI mice, and was inhibited after administration of GA (Fig. 3). Subsequently, the apoptotic biomarkers bax and CC3 were detected. Bax positive cell number elevated in the brain of TBI mice, and was inhibited by GA treatment (Fig. 4). CC3 positive cell number also raised in the brain of TBI mice, and was attenuated by administrating of GA (Fig. 5).

4.4. GA attenuated oxidative stress in the brain of mice after TBI

Firstly, oxidative stress was detected at 7 days after TBI. One of the oxidative stress biomarker, 8-OHdG, raised in the brain of TBI mice, and was inhibited by administrating of GA (Fig. 6a-c). The level of MDA was higher in TBI mice, and decreased after GA treatment (Fig. 6d). The level of SOD activity reduced in TBI mice, and was reversed after GA administration (Fig. 6e). Secondly, oxidative stress was detected at 3 days after TBI. The increase of MDA (Fig. 6f) and the decrease of SOD activity (Fig. 6g) were reversed after treating with GA.

5. Discussion

Traumatic brain injury (TBI) manifests in many forms, ranging from mild changes in consciousness to sustained coma and death. The entire brain is affected by diffuse damage and swelling in the most severe form of TBI [19]. TBI causes damage to the central nervous system (CNS) through various mechanisms, including synaptic dysfunction, mitochondrial dysfunction, neuroinflammation, protein aggregation,and oxidative stress [20]. EGb761 is an extract of Ginkgo biloba leaves which has been standardized and widely studied. Ginkgolides and ginkgolides are important components of EGb761 and have protective effects on brain injury [21]. The primary findings of this study were that GA administration could restore neurobehavioral function and attenuated raises of apoptosis and oxidative stress in TBI mice.

The pathology of TBI is heterogeneous and complex. TBI is usually divided into primary and secondary injuries. Primary injury is caused by mechanical forces during injury. The type and severity of injury depend on the nature, location, and direction of the initial force [22]. After mechanical injury, a series of cellular and biochemical changes, including inflammation, oxidative stress, mitochondrial dysfunction and apoptosis, begin within a few minutes and lead to secondary damage, which can even last for months to years [23]. Nevertheless, there is still no specific drug for the damages caused by TBI despite the effectiveness of current experiments and clinical treatments [24,25]. Therefore, developing effective and innovative treatment strategies to treat traumatic brain injury remains a top priority. We present found that GA administration improves mNSS scores, Grid-Walking test and Rotarod test of TBI mice. These findings indicated that GA could improve neurobehavioral deficiency of mice induced by TBI.

Cell death is one of the important mechanisms for maintaining lifelong tissue homeostasis and plays a crucial role in brain tissue damage, behavior and memory disorders after acute brain injury. Apoptosis often occurs after TBI [26,27]. TBI induced brain tissue damage, neurological function deficits as well as neural apoptosis [28]. GA could attenuate numerous cell apoptosis in many diseases, including neuroprotective effects [21,29]. Current study indicated that TBI induced tunel positive cells increase, and was inhibited by GA administration. Moreover, the apoptotic biomarkers such as Bax and CC3 raised in TBI mice and weakened after administration of GA. These results demonstrated that GA significantly improved cell apoptosis in the brain of TBI.

Oxidative stress has been related to a variety of diseases and involved in the first appearance and/or progression of several neurodegenerative disorders [30]. Several studies have been conducted to find the role of ROS in the evolution of neurodegenerative diseases, with promising results. The research results have indicated that reactive oxygen species are not triggering factors for these diseases, and they may exacerbate disease progression due to oxidative damage and interactions with mitochondria [31,32]. ROS-related oxidative damage and neuronal apoptosis are important pathogenesis of secondary brain injury after traumatic brain injury [33,34]. As is well known, inhibiting oxidative stress and cell apoptosis are some potential mechanisms of anti-ischemic drugs, and ginkgolides can achieve this [35]. We present found that 8-OHdG, a biomarker of oxidative stress [36], raised in TBI mice, and was inhibited by GA administration. After treatment of GA, the increase of MDA and the decrease of SOD in the brain of TBI were also reversed. Our results indicated that GA alleviated TBI by reducing oxidative stress.

There are two limitations in this present study. Firstly, we found GA administration significantly alleviated the apoptosis in the brain of TBI mice. However, the apoptotic pathways are still unclear. Previous reviews have summarized ginkgolides alleviated many related apoptosis pathway, as evidenced by decreasing *p*-JNK, p-PERK, p-IRE1α, ATF6, C/EBP homologous protein, toll-like receptor 4/nuclear factor kappa-B, and the PI3K/Akt pathways in several diseases [21,37,38]. In the future, we will explore which pathways are involved in the regulation of GA on the apoptosis in the brain of TBI mice. Secondly, endoplasmic reticulum stress modulator such as docosahexaenoic acid (DHA) [39], or additional oxidative stress modulators such as lipoic acid [40] can be as therapeutic for prevention of chronic traumatic encephalopathy. We will further investigate how GA can be combined with DHA or lipoic acid.

6. Conclusion

We found that GA treatment could improve neurological functions of TBI mice. Administration of GA alleviated neurological function by reducing cell apoptosis and oxidative stress of TBI mice. GA could be a drug for TBI therapy in the future.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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CRediT authorship contribution statement

Lei Zhu: Writing – original draft, Investigation. **Zhengwei Li:** Writing – original draft, Methodology. **Liping Sheng:** Resources. **Fengfei Zhang:** Conceptualization. **Wei Ji:** Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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