**RESEARCH ARTICLE**

# Ampelopsin alleviates sevoflurane-induced cognitive dysfunction by mediating NF-κB pathway in aged rats

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## Abstract

**Background** Cancer-induced bone pain (CIBP) is the pain caused by bone metastasis from malignant tumors, and the largest source of pain for cancer patients. miR-300 is an important miRNA in cancer. It has been shown that miR-300 regulates tumorigenesis of various tumors.

**Purpose** This study aims to investigate the role of miR-300 in CIBP and its underlying molecular mechanisms in vitro and in vivo.

**Methods** We constructed CIBP model in rats and investigated the mechanism through which miR-300 affects CIBP. We first examined expression level of miR-300 in CIBP rats and then tested the effect of its overexpression. Next, we identified the target of miR-300 using TargetScan analysis and double luciferase assay. Finally, we studied genetic interactions between miR-300 and its target and their roles in CIBP.

**Results** We found that miR-300 was downregulated in CIBP rats. Overexpression of miR-300 significantly attenuated cancer-induced neuropathic pain (p < 0.01). Furthermore, TargetScan analysis and double luciferase assay show High Mobility Group Box 1 (HMGB1) is a target of miR-300. Notably, HMGB1 is overexpressed in CIBP rats, while up-regulation of miR-300 significantly suppresses expression of HMGB1 (p < 0.01). Moreover, knockdown of HMGB1 by siRNA significantly relieves cancer-induced neuropathic pain in rats (p < 0.01). On the other hand, HMGB1 overexpression partially blocked the effect of miR-300 on cancer-induced nerve pain.

**Conclusion** miR-300 relieves cancer-induced neuropathic pain by inhibiting HMGB1 expression. These results may be beneficial for the treatment of CIBP in clinical practice.

**Keywords** Ampelopsin · Sevoflurane · Cognitive dysfunction · NF-κB pathway

## Introduction

Post-operative cognitive dysfunction (POCD) is the impairment of neurocognitive function after anesthesia and surgery, which featured by abnormal mentality, personality and memory (Hovens et al. 2014). For the incidence of POCD, anesthesia methods and aging were considered as the major

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risk factors (Jungwirth et al. 2009). Compared with intravenous anesthesia, inhalation anesthesia causes higher occurrence of POCD (Tang et al. 2014). Therefore, as the most widely used inhalation anesthetic, sevoflurane-induced cognitive dysfunction has got the priority in POCD researches. Sevoflurane has been identified to induce neuroinflammation and neuronal apoptosis, which play essential roles in the pathogenesis of POCD (Rosczyk et al. 2008; Vacas et al. 2013; Wan et al. 2007).

Many studies focused on the effects of Traditional Chinese Medicine (TCM) monomers in POCD. For example, tetrandrine, a bisbenzylisoquinoline alkaloid, has been reported to alleviate sevoflurane-induced cognitive dysfunction by inhibiting neuroinflammation and neural apoptosis in aged rats (Ma et al. 2016). In isoflurane-induced cognitive dysfunction, Apigenin could restore histone acetylation and restrain neuroinflammation to attenuate the symptoms of POCD (Chen et al. 2017). Berberine, an isoquinoline alkaloid, reduces the levels of proinflammatory cytokines in neurons and thereby ameliorates surgery-induced cognitive dysfunction (Zhang et al. 2016). Generally, TCM has potential applications in prevention and treatment of POCD.

Ampelopsin, also called dihydromyricetin, is one kind of flavonoids derived from *ampelopsis grossedentata*, an edible-medicinal herb mainly grown in southern China (Kou et al. 2016). Ampelopsin has been shown to possess some pharmacological activities including antioxidant, anti-inflammatory, anticancer and antimicrobial effects (Zhou et al. 2014; Hou et al. 2014; Qi et al. 2012). Ampelopsin was reported to inhibit inflammatory responses through PI3K/AKT/NF-κB pathways (Qi et al. 2012). Moreover, ampelopsin protects PC12 cells against 6-OHDA and $H_2O_2$ induced neurotoxicity via GSK-3β/NRF2/ARE and ERK/AKT signaling (Kou et al. 2012, 2015). Based on previous studies, it is reasonable to hypothesize that ampelopsin may execute protective effects in POCD patients.

In the present study, the effects of ampelopsin on cognitive deficits induced by sevoflurane in aged rats were evaluated. Besides, neuroinflammation, neural cell apoptosis and NF-κB signaling were determined to elucidate the underlying mechanisms. Overall, ampelopsin is a promising therapeutic TCM for POCD induced by inhaled anesthetics.

## Materials and methods

### Animals and ethics

20-month-old male Sprague–Dawley rats were purchased from Shanghai SLAC Laboratory Animal Co., Ltd (Shanghai, China). These rats were raised in specific pathogen free environment with constant temperature (22°±2°), humidity (60±5%) and 12 h light–dark cycle. All rats were acclimated

in animal rooms for at least 7 days prior to the experiments. All experimental protocols for rats accorded with Medicine Ethics Review Committee for Animal Experiments.

### Animal grouping and treatment

A total of 40 male Sprague–Dawley rats (20-month-old, 500 ± 150 g) were assigned to four groups (n = 10): (1) Control group (Control), rats intraperitoneally injected with normal saline (0.1 ml/100 g); (2) Ampelopsin group (Amp), rats intraperitoneally injected with ampelopsin (40 mg/kg, every 3 days for 4 weeks; ChemFaces, Wuhan, China); (3) Sevoflurane group (sef), rats inhaled 2% sevoflurane (Hengrui Pharmaceutical, Shanghai, China) for 5 h and intraperitoneally injected with normal saline (0.1 ml/100 g); (4) Sevoflurane + ampelopsin group (sef + Amp), rats inhaled 2% sevoflurane for 5 h and then intraperitoneally injected with ampelopsin (40 mg/kg, every 3 days for 4 weeks).

Rat anesthesia model was established as follows: 2% sevoflurane was used to anesthetize rats for 5 h. The gas flow rate was set at 1.5 L/min and 70% $O_2$ was used as a carrier. After anesthesia, rats were observed and maintained separately.

### Morris water maze (MWM) test

Following ampelopsin treatment for 4 weeks, the cognitive functions of sevoflurane-treated rats were evaluated with MWM test (Ma et al. 2016). MWM includes a cylindrical pool (150 cm in diameter, 60 cm in depth, divided into four identical quadrants) filled with water (25°±1°, 30 cm in depth) and a hidden platform (10 cm in diameter, 1 cm beneath the water) located in one fixed quadrant. The test lasted 5 days and rats were measured 4 times/day. Rats were gently put into water at random starting positions (facing the wall of pool). Escape latency was recorded as the time to find the hidden platform and mean path length stood for the average movement distance of each rat. On the 5th day, the hidden platform was taken away and rats were released into water for 60 s. The numbers of crossing the determinate quadrant and the time of staying determinate area was recorded. Rats tested in MWM test were not used for CFC test.

### Context fear conditioning (CFC) test

One day before CFC test, tone cued conditioning training was performed for each rat (Yang and Yuan 2018). At the start, rats were put in the test box and acclimatized to the surroundings for several minutes. A conditioned tone (70 dB, 20 s) and 25 s later an unconditioned foot shock (0.7 mA, 2 s) were given to the rats. Above operation was repeated for 6 times (1 min interval time) and the freezing time of each

rat was recorded. Two days after stimulus, fear conditioning memory was assessed. Rats were put in the same box for 5 min without conditioned tone and unconditioned foot shock and the freezing time of each rat was recorded. Rats tested in CFC test were not used for MWM test.

## Hippocampus tissue preparation

Rats were anesthetized with 10% chloral hydrate (0.3 ml/100 g, intraperitoneal injection) and executed. Hippocampus was quickly removed, divided into four parts and stored in liquid nitrogen. For RNA extraction, harvested hippocampus tissues were washed with PBS, cut into pieces and then homogenized in TRIzol (Invitrogen, Carlsbad, USA). For protein extraction, harvested hippocampus tissues were washed with PBS, cut into pieces and then homogenized in RIPA lysis buffer (Beyotime, Shanghai, China). Nuclear and Cytoplasmic Extraction Reagents (Thermo Fisher Scientific, Waltham, USA) were used to extract the nucleoproteins in hippocampus.

## Real time PCR

Total RNA was obtained by RNeasy Plus Universal Mini Kit (QIAGEN, Venlo, Netherlands) and reverse transcribed into cDNA using PrimeScript™ RT reagent Kit (Takara, Shiga, Japan). Real time PCR was carried out with ABI 7900 Real-Time PCR system (Applied Biosystems, Foster City, USA) using SYBR Select Master Mix Kit (Life Technologies, Carlsbad, USA). Primers of IL-1β, IL-6, TNFα and GAPDH are listed in Table S1.

## Enzyme-linked immunosorbent assays (ELISAs)

The homogenate of hippocampus was centrifuged at 4° (12,000 g, 15 min) and the supernatant was collected. Cytokine ELISA Kits (R&D Systems, Minneapolis, USA) were used to measure IL-1β, IL-6 and TNF-α levels following the manufacturer's instructions.

## Measurement of caspase activity

Harvested hippocampus tissue was washed with PBS, cut into pieces and then homogenized in lysis buffer from Caspase Activity Detection Lit (Beyotime, Shanghai, China). Mixture containing 50 μl supernatant, 10 μl Ac-DEVD-pNA (2 mM) and 40 μl diluent was incubated for 1 h at 37°. The activities of caspase-3 and caspase-9 were determined at 405 nm absorbance.

## Western blot

The homogenate of hippocampus was centrifuged at 4° (12,000 g, 15 min) and the protein concentration in supernatant was detected with BCA Protein Assay Kit (Beyotime, Shanghai, China). Sodium dodecyl sulfate (SDS)—polyacrylamide gel electrophoresis (PAGE) was used to separate proteins, which were then transferred onto PVDF membranes (Millipore, Billerica, USA). After blocked in skim milk solution (5%) for 2 h, membranes were incubated overnight at 4° with primary antibodies anti-cleaved caspase-3 (Asp175), cleaved caspase-9 (Asp315), cleaved PARP (Asp214), IκBα (L35A5), Phospho-IκBα (Ser32), p65, GAPDH and Laminb (CST, Danvers, USA). Then, secondary antibodies conjugated with HRP (Beyotime, Shanghai, China) were added for incubating 1 h. Super-Signal West Dura Extended Duration Substrate (Thermo Fisher Scientific) and ImageQuant LAS 4000mini (GE Healthcare Life Scicences) were used to visualize the expression of target proteins.

## Statistical analysis

All experiments were repeated three times and results were shown as $M \pm SD$ (mean ± standard deviation). Statistical analysis for comparison was performed with One-way analysis of variance (ANOVA; SPSS 16.0) and $p < 0.05$ was considered as statistically significant difference.

# Results

## Ampelopsin ameliorated cognitive deficits induced by sevoflurane in aged rats

To explore the effects of ampelopsin on cognitive deficits, sevoflurane-induced cognitive dysfunction in aged rats was established. Subsequently, MWM test and CFC test were used to measure the learning and memory ability. In MWM test, significant cognitive impairment in rats was induced by sevoflurane anesthesia, including the elevation in escape latency and path length, the decrease in numbers of crossing platform and time spent in target quadrant (Fig. 1a, $p < 0.01$). However, these symptoms of sevoflurane-induced cognitive dysfunction were markedly alleviated when treated with ampelopsin simultaneously (Fig. 1a, $p < 0.01$).

Similarly, reduced immobility (freezing time) of rats was observed after sevoflurane inhalation in CFC test, which was partially restored by ampelopsin treatment (Fig. 1b, $p < 0.01$). Additionally, control group and ampelopsin group showed no significant differences in both MWM test and CFC test (Fig. 1a, b). These results showed that ampelopsin
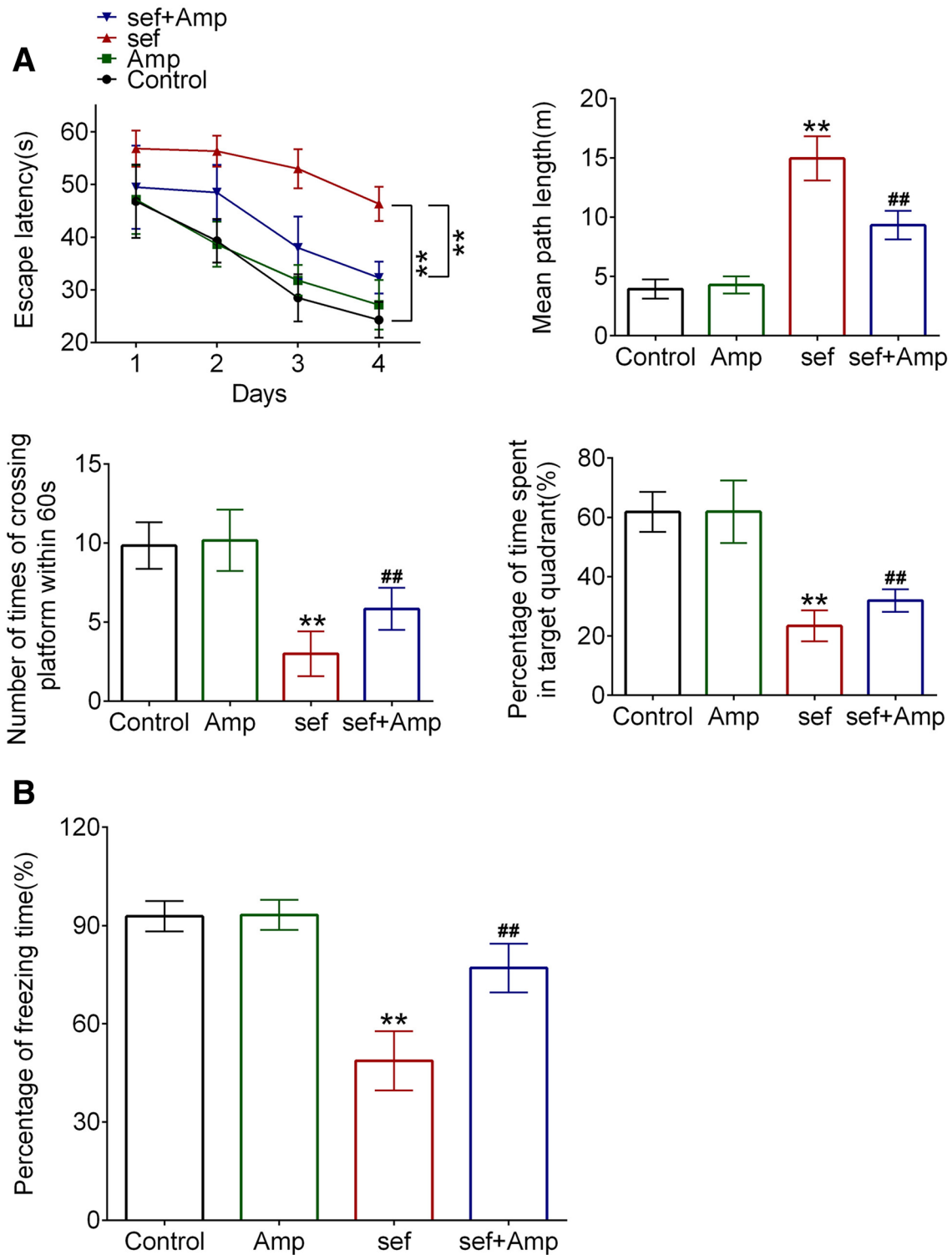
**Fig. 1** Ampelopsin ameliorated cognitive deficits induced by sevoflurane in aged rats. **a** Comparison of latency escape (for 1–4 days), path length (mean), numbers of crossing platforms (within 60 s) and time spent in target quadrant (percentage) in MWM test. **b** Comparison of freezing time (percentage) in CFC test. $**p < 0.01$ versus control group; $\#\#p < 0.01$ versus sef group
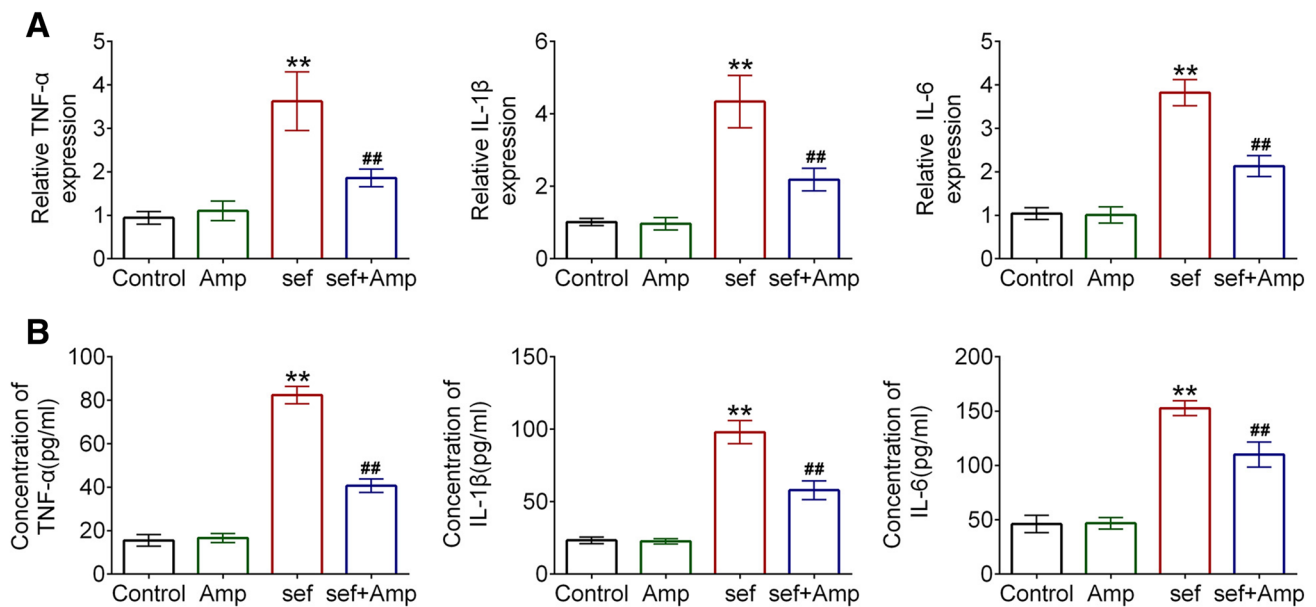
**Fig. 2** Ampelopsin reduced the levels of cytokines induced by sevoflurane in aged rats. **a** The mRNA expression of TNFα, IL-1β and IL-6 in hippocampus of rats. **b** the levels of pro-inflammatory cytokines TNFα, IL-1β and IL-6 in hippocampus of rats. **$p < 0.01$ versus control group; ##$p < 0.01$ versus sef group

ameliorated the learning and memory dysfunction induced by sevoflurane in aged rats.

## Ampelopsin reduced the levels of cytokines induced by sevoflurane in aged rats

To investigate the anti-neuroinflammation effects of ampelopsin, the expression levels of pro-inflammatory cytokines (such as IL-1β, IL-6 and TNFα) in hippocampus were determined. After sevoflurane anesthesia, both the mRNA expressions and protein levels of TNFα, IL-1β and IL-6 were remarkably higher than that in control group (Fig. 2a, b, $p < 0.01$). In contrast, sevoflurane + ampelopsin group showed decreased mRNA expressions and protein levels of TNFα, IL-1βand IL-6 when compared with sevoflurane group (Fig. 2a, b, $p < 0.01$). there was no significant difference between control group and ampelopsin group (Fig. 2a, b). these data suggested that ampelopsin suppressed neuroinflammation induced by sevoflurane via reducing the levels of pro-inflammatory cytokines.

## Ampelopsin suppressed neural cell apoptosis induced by sevoflurane in aged rats

To evaluate the regulatory role of ampelopsin in neural cell apoptosis, the activities of pro-apoptotic proteins caspase-3 and caspase-9 in hippocampus were examined. Compare with control group, sevoflurane markedly enhanced the

activities of caspase-3 and caspase-9 (Fig. 3a, $p < 0.01$). However, ampelopsin treatment significantly lowered the enhancement of caspase-3 and caspase-9 activities in aged rats anesthetized with sevoflurane (Fig. 3a, $p < 0.01$).

To further support these findings, the expressions of apoptosis markers (cleaved caspase-3, cleaved caspase-9 and cleaved PARP) were detected with western blot. Corresponding to the above results, ampelopsin effectively suppressed the sevoflurane-induced overexpression of cleaved caspase-3, cleaved caspase-9 and cleaved PPAR (Fig. 3b, $p < 0.01$). Both the activities and expressions of caspase-3 and caspase-9 showed no statistical difference between control group and ampelopsin group (Fig. 3a, b). These results indicated that ampelopsin exhibited anti-apoptotic effects in sevoflurane-induced neural cell apoptosis.

## Ampelopsin inhibited the activation of NF-κB pathway induced by sevoflurane in aged rats

To explore the molecular mechanisms underlying the protection of ampelopsin against sevoflurane-induced cognitive impairment, we focused on the NF-κB signaling pathway which is the essential part in the regulation of inflammation. In sevoflurane group, the phosphorylation level of IκBα and protein expression of nucleus p65 were significantly increased in hippocampus (Fig. 4). However, both IκBα phosphorylation and nucleus p65 expression induced by sevoflurane were blunt with the treatment of ampelopsin (Fig. 4). In addition, NF-κB pathway was not activated in
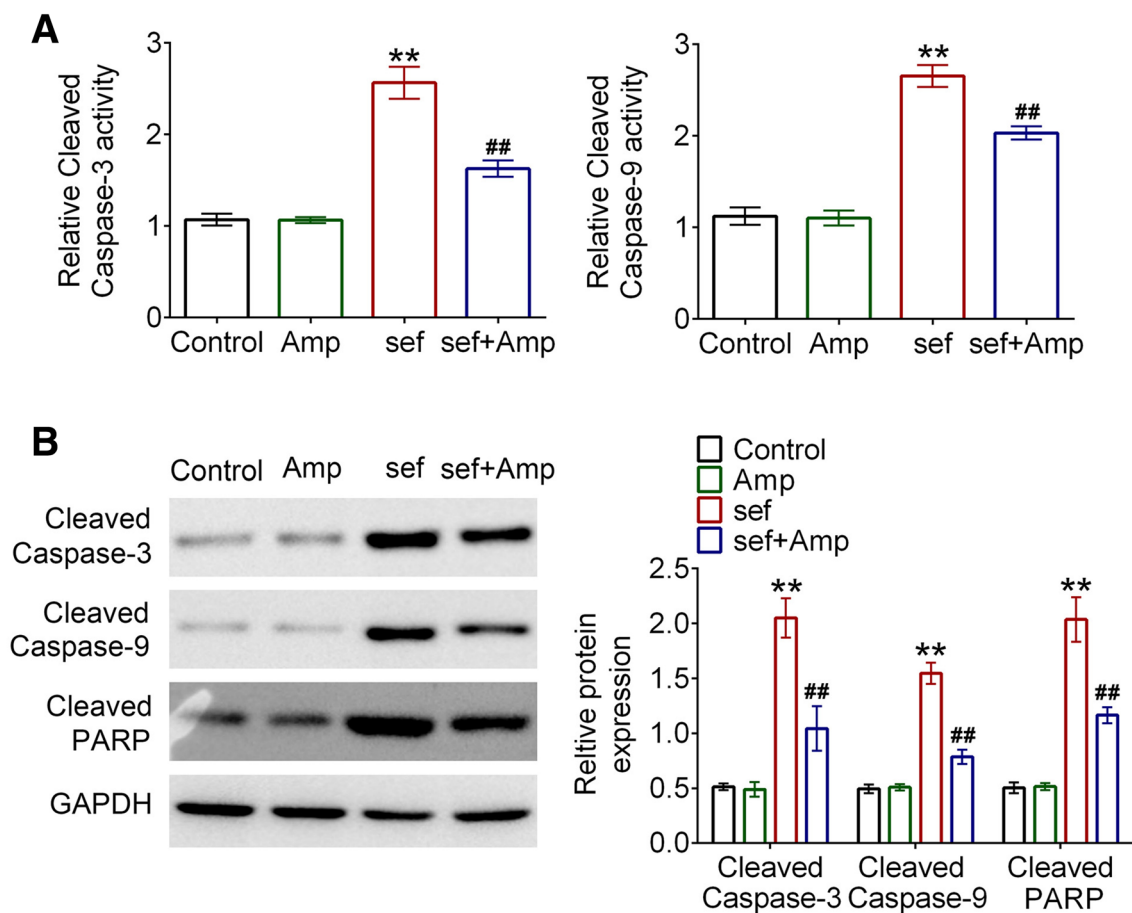
**Fig. 3** Ampelopsin suppressed neural cell apoptosis induced by sevoflurane in aged rats. **a** The activity of caspase-3 and caspase-9 in hippocampus of rats. **b** The active forms of apoptosis-associated proteins including cleaved caspase-3, cleaved caspase-9 and cleaved PARP were determined. **p<0.01 versus control group; ##p<0.01 versus sef group
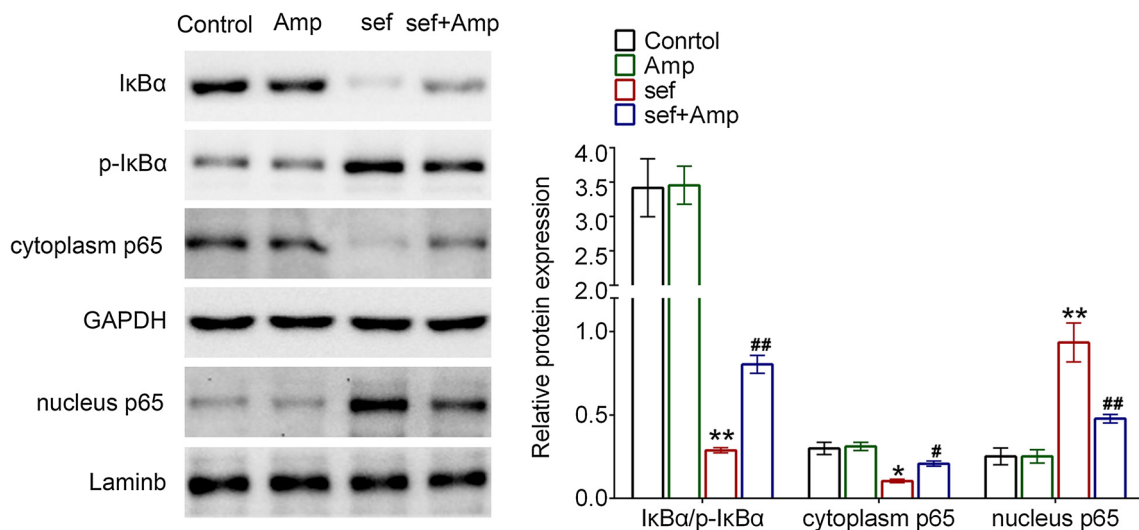


**Fig. 4** Ampelopsin inhibited the activation of NF-κB pathway induced by sevoflurane in aged rats. The expressions of NF-κB pathway-related proteins such as phosphorylated IκBα and nucleus p65 were evaluated. *p<0.05, **p<0.01 versus control group; #p<0.05, ##p<0.01 versus sef group

both control group and ampelopsin group (Fig. 4). In summary, the suppression of neuroinflammation and neural cell apoptosis in sevoflurane-treated rats by ampelopsin are at least partly attributed to the regulaiton of NF-κB pathway.

## Discussion

Hippocampus is responsible for cognitive function, including memory and learning (Liu and Yin 2018). MWM test and CFC test are classic experiments widely used in the investigation of cognitive impairment to assess the spatial learning and memory abilities of laboratory animals (Del Rosario et al. 2012; Hobin et al. 2003). Previous study has showed anesthesia with 2% sevoflurane for 2 h could induce hippocampal impairment in rats, which is consistent with our results in MWM test and CFC test (Zhu et al. 2017). In this study, ampelopsin treatment markedly alleviated the phenotypes of anesthetized rats in MWM test and CFC test, suggesting the protective effect of ampelopsin on hippocampal impairment induced by sevoflurane.

Neuroinflammation, particular in hippocampus, makes chief contribution to the progression of POCD, which mainly attributes to the cytokines produced by immune cells in central nervous system (Liu and Yin 2018; Safavynia and Goldstein 2018; Feng et al. 2017). In hippocampus, astrocytes could be stimulated to release pro-inflammatory cytokines, including IL-1β, IL-6 and TNFα, triggering neuroinflammation and inducing cognitive impairment (Tan et al. 2014). Moreover, high levels of proinflammatory cytokines enhance excitotoxicity and lead to memory impairment (Bernardino et al. 2005). The inhibition of cytokines have been proved as an effective manner for alleviating POCD (Liu and Yin 2018). In current study, ampelopsin restored the elevated levels of pro-inflammatory cytokines in anesthetized aged rats. Similarly, ampelopsin have been found to inhibit the enhanced levels of cytokines in microglia induced by LPS (Weng et al. 2017). Therefore, ampelopsin may alleviate sevoflurane-induced cognitive dysfunction via attenuating neuroinflammation.

Neurons in hippocampus are the key cells in learning and memory (Liu and Yin 2018). Neuronal apoptosis has been considered as a direct factor for POCD development (Vacas et al. 2013). Neural cell apoptosis induced by sevoflurane results in the impairment of cognitive ability in rats (Chen et al. 2013). Caspase cascade has been proved as an essential part of cell apoptosis (Whyte and Evan 1995). In cells undergoing apoptosis, caspase-3, caspase-9 and their substrates such as PARP are activated through cleavage, which amplifying chain reaction to degrade cellular components (Shalini et al. 2015). In this study, sevoflurane inhalation leaded to the activation of caspase cascade in the hippocampus of rats,

which was markedly reversed by ampelopsin. In sympathetic PC12 cells, $H_2O_2$-induced apoptosis could be inhibited by ampelopsin (Kou et al. 2012). Taken together, ampelopsin could prevent neural cell apoptosis, which is proposed as a feasible strategy for restoring cognitive function after sevoflurane treatment (Wang and Zuo 2015).

NF-κB signaling pathway has an essential role in immune responses and could be activated after the treatment of anesthetics (Li et al. 2013). Once stimulated, NF-κB signaling is activated by phosphorylation and translocating p65 into nucleus to promote the expressions of pro-inflammatory cytokines (Vallabhapurapu and Karin 2009). NF-κB signaling also regulates neuronal survival via atypical protein kinase (Wooten 1999). Therefore, the inhibition of NF-κB signaling has been shown to alleviate anesthesia-induced cognitive impairment (Ma et al. 2016; Zhang et al. 2014; Tian et al. 2015). Moreover, the activation of NF-κB signaling induced by LPS and ROS all could be reduced by ampelopsin (Qi et al. 2012; Weng et al. 2017). In present study, NF-κB signaling in hippocampus was activated by sevoflurane anesthesia, which was inhibited by ampelopsin. Taken together, ampelopsin ameliorated neuroinflammation and neural cell apoptosis may depend on the suppression of NF-κB signaling. However, other signaling pathways may involve in the protective effects of ampelopsin and more investigations need to be done.

## Conclusion

In summary, this study demonstrated that ampelopsin remarkably improved sevoflurane-induced cognitive dysfunction in aged rats via attenuating neuroinflammation, preventing neural cell apoptosis and inhibiting NF-κB signaling. These results highlight that ampelopsin is a promising TCM for the treatment of POCD induced by inhaled anesthetics.

## Compliance with ethical standards

**Ethics approval and consent to participate** The animal use peotocol listed below has been reviewde and approved by the Animal Ethical and Welfaer Committee (Approval No. 20190004).

**Patient consent for publication** Not Applicable.

**Informed consent** Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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