

Schisandrin Inhibits NLRP1 Inflammasome-Mediated Neuronal Pyroptosis in Mouse Models of Alzheimer's Disease

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Quan Li¹
Qi Wang²
HuiBo Guan³
Yanyan Zhou²
Li Liu⁴

¹Department of Organs, First Affiliated Hospital, Heilongjiang University of Chinese Medicine, Harbin 150040, Heilongjiang, People's Republic of China;

²Teaching and Research Department of Basic Theory of Traditional Chinese Medicine, Heilongjiang University of Chinese Medicine, Harbin 150040, Heilongjiang, People's Republic of China;

³Teaching and Research Department of Diagnostics of Traditional Chinese Medicine, Heilongjiang University of Chinese Medicine, Harbin 150040, Heilongjiang, People's Republic of China;

⁴Department of Cardiovascular Diseases, First Affiliated Hospital, Heilongjiang University of Chinese Medicine, Harbin 150040, Heilongjiang, People's Republic of China

Background: In recent years, schisandrin (SCH) was proved to improve Alzheimer's Disease (AD). The aim of our study is to explore the effect of SCH on neuronal pyroptosis in the disease.

Methods: A Morris water maze test was performed to evaluate the spatial learning and memory retention of AD mouse. ELISA was fulfilled to examine the concentration of A β , IL-1 β , and IL-18. Western blot was performed to detect the expression of apoptosis- and pyroptosis-related proteins. Besides, the neuronal apoptosis rate was examined using TUNEL assay. Immunohistochemistry was utilized to detect the activation of NLRP1 inflammasome.

Results: Here, AD mice have serious cognitive impairment. Meantime, A β was highly expressed in the brains of AD mice. SCH could effectively rescue the cognitive impairment in AD mice and impede the production of A β . Subsequently, we further demonstrated that SCH repressed neuronal apoptosis, pyroptosis-related proteins expression, and the activation of NLRP1 inflammasome in the hippocampus of AD mice. We also proved that A β induced neuronal apoptosis and pyroptosis in vitro. However, the effects of A β on neuronal apoptosis and pyroptosis were partly reversed by SCH treatment.

Conclusion: Overall, our data indicated that SCH improved cognitive impairment in AD mice through inhibition of NLRP1 inflammasome-mediated neuronal pyroptosis and neuronal apoptosis. Our works provided new evidence to support SCH acting as a potential treatment method in AD.

Keywords: Alzheimer's disease, pyroptosis, schisandrin, apoptosis, traditional Chinese medicine

Introduction

Alzheimer's disease (AD) is an irreversible neurodegenerative disease associated with human aging. Healthcare cost of the patients with AD has continuously increased, resulted in a significant economic burden.¹ Worryingly, there have been no new drugs approved by the US Food and Drug Administration for AD treatment since 2003. Hence, relieving symptoms and slowing symptom progression are still the major goals of existing AD treatments.² The clinical features of AD patients included progressive decline of learning and memory function and subsequent loss in cognitive function, caused by the excessive accumulation of amyloid- β (A β) peptide and tau protein.³ Moreover, obvious loss of neuron and neuropathologic lesions were found in multiple brain regions of patients

Correspondence: Li Liu
Department of Cardiovascular Diseases,
First Affiliated Hospital, Heilongjiang
University of Chinese Medicine, No. 26
Heping Road, Xiangfang District, Harbin
150040, Heilongjiang, People's Republic of
China
Tel +86 451-82111401 Ext 6975
Email liuli_hucm@126.com

with AD.^{4,5} It was proved that interleukin 1 β (IL-1 β)-mediated inflammation response plays an important role in the pathogenesis of AD.⁶ However, the clearly molecular mechanism of neuronal loss in AD is still unknown.

Pyroptosis, a programmed cell death pathway discovered in recent years, is an inflammatory form of cell death triggered by activated inflammasomes, including the NOD-like receptor (NLR) family (NLRP3, NLRP1, NLRP4).⁷ Pyroptosis involves two mainly pathways: the classical caspase-1-dependent pathway and non-classical caspase-4- and caspase-5-dependent pathways. For the canonical caspase-1-dependent pathway, activated inflammasomes can bind to adaptor protein apoptosis-associated speck like proteins (ASC) and activate caspase-1. Then cell pyroptosis was induced by pro-IL-1 β and pro-IL-18 processing, and cleavage of gasdermin D (GSDMD).⁸ It was reported that pyroptosis is closely associated with the pathogenesis of many human disorders, such as cardiovascular diseases and sepsis.⁹ Recently, Tan et al¹⁰ found that the expression of NLRP1 is increased in cerebral of AD transgenic mice, A β ₁₋₄₂ induces caspase-1-dependent pyroptosis of cortical neuron via activation of NLRP1. In addition, Zhao et al¹¹ revealed that amentoflavone could effectively reduce A β ₁₋₄₂-induced neurological dysfunction of an AD animal model via suppression of neuronal pyroptosis by targeting AMPK/GSK3 β signaling. These results prompt that A β -induced neuronal pyroptosis is a potential pathogen of AD.

As a traditional Chinese medicine (TCM), *Schisandra chinensis* (Turcz.) Bail. (*S. chinensis*), native chiefly to northeastern China, Korea, eastern Russia, and Japan, and was utilized against multiple disorders like autoimmune disease, cardiovascular disease, acne, as well as neurological disease.¹² Currently, the chemical composition of *S. chinensis* is still not fully known. Dibenzo[a,c]cyclooctadiene lignans, also named as schisandra lignans, are the most important components of *S. chinensis* berries.¹³ Growing evidence has indicated that *S. chinensis* has anti-cancer, anti-inflammatory, hepatoprotective, anti-bacterial, and multiple other activities.¹⁴ Schisandrin (SCH) and schizandrol are the representative lignans of *S. chinensis*. The anti-inflammatory effect of them has already been reported in a number of studies.¹⁵ It was reported that SCH notably suppresses *propionibacterium acnes*-induced pyroptosis of THP-1 cells through obstructing the activation of NLRP3 inflammation and secretion of IL-1 β .¹⁶ In addition, it was revealed that SCH plays a protective role in AD.¹⁷ This present

study proved that SCH obviously improved the learning and memory functions in an AD mouse model. Mechanistically, SCH repressed A β -induced NLRP1-mediated neuronal pyroptosis and subsequent neuronal apoptosis, thus improving AD.

Materials and Methods

Animals and Groups

APP/SP1 double transgenic mice (B6.Cg-Tg(*APP*^{Swe}, *PSEN1*^{ΔE9})85Dbo/Mmjax) expressing chimeric mouse/human APP with Swedish familial mutations and mutant human Presenilin-1, and their age- and background-matched C57BL/6 wide-type (WT) mice were obtained from the Model Animal Research Center of Nanjing University (Nanjing, China). All mice were housed in a controlled environment with enough water and food. The ethical approval for this study was obtained from the First Affiliated Hospital, Heilongjiang University of Chinese Medicine (No20200212c0230120 [101]). All animal care and experimental procedures conformed to the Standard Medical Laboratory Animal Care and Use Protocols (Ministry of Health PR China, 1998) and the Laboratory Animal Ethical Standards of First Affiliated Hospital of Heilongjiang University of Chinese Medicine.

Twelve-month-old mice were randomly divided into three groups (n=6 per each group): WT group, AD group, and AD+SCH group. C57BL/6 WT mice served as blank control. The mice in the AD+SCH group were administered SCH (2 mg/kg/day, Weikeqi Biological Technology Company, Ltd., Sichuan, China) by means of intragastric administration for 2 weeks. The mice in the AD group were given the same volume of distilled water for 2 weeks.

Morris Water Maze Test

The Morris Water Maze (MWM) behavioral test was performed to examine the spatial learning and memory abilities of mice. At 2 weeks later for SCH treatment, all mice were administered the MWM test for 6 consecutive days, as previously described.¹⁸ The MWM test includes a navigation test and a probe trial test. The apparatus consisted of an opaque circular water tank (90 cm in diameter $\times$ 50 cm in height, Beijing Sunny Instruments Co. Ltd., Beijing, China) with an escape platform (4.5 cm in diameter) placed in the midpoint of IV quadrant (target quadrant) and submerged 1 cm below the water surface. From day 1 to day 5, the escape platform was placed

under the water for the navigation test. Each mouse were subjected to four trials every day. The escape latency, the time between a mouse being put into the water and climbing onto the platform, and path length for each mouse were recorded. Each mouse was left to find the platform for 60 seconds. If it failed, the mouse would be placed on the platform for 60 seconds. On day 6, the platform was removed, and the mouse was put into the water from the opposite side of the target quadrant. Each mouse were allowed to swim freely for 60 seconds before the experiment. The percentage of time that each mouse spent in the target quadrant and the number of times each mouse crossed the center of the target quadrant were recorded.

ELISA Assay

The concentration of $A\beta_{1-42}$ and $A\beta_{1-40}$ in brain tissues, IL-1 β and IL-18 in hippocampus tissues, and IL-1 β and IL-18 in cell culture medium were examined by using ELISA assay. The Beta Amyloid x-40 and x-42 ELISA kits were purchased from Covance. IL-1 β and IL-18 ELISA kits were from R&D Systems (Minneapolis, MN, USA). All experiments were carried out in accordance with the manufacturer's instructions.

TUNEL Assay

The apoptosis rate of hippocampus neurons in each mouse and SH-SY5Y cells were measured by using TUNEL assay (In Situ Cell Death Detection Kit, POD; Roche). For the tissue samples, tissues were fixed with 4% paraformaldehyde at 4°C overnight. Next, paraffin-embedded tissues were sliced into 4 μ m-thick sections, which were then treated with dewaxing and hydration. After that, the sections were maintained with proteinase-K (20 μ g/mL) for 15 minutes at room temperature. Then, the sections were incubated with 2% H_2O_2 for 5 minutes, TUNEL working solution for 1 hour at 37°C in the dark, stop solution for 30 minutes at 37°C, peroxidase-streptavidin conjugate solution for 30 minutes at room temperature, and fresh DAB solution for 5 minutes. Lastly, the sections were stained with hematoxylin staining solution. For the cell samples, cells were fixed with 4% paraformaldehyde for 30 minutes at 4°C, and washed with 0.01 M PBS twice. Next, the cells were maintained with 50 μ L TUNEL solution for 1 hour at 37°C, and incubated with DAPI staining solution for 5 minutes at room temperature. Finally, a fluorescence microscope (Olympus, BX51) was used to examine the number of TUNEL-positive cells.

Western Blotting Assay

RIPA lysis buffer was utilized to isolate the total protein from hippocampus tissues and cells. After detection of the protein concentration, equal amounts of protein (20 μ g) were separated on 12% SDS-PAGE gel, and then were transferred onto PVDF membranes. Next, membranes were blocked with 5% non-fat milk for 1 hour at room temperature and subsequently incubated with primary antibodies against NLRP1 (1:2,000, Santa Cruz, CA), ACS (1:1,000, Santa Cruz), cleaved caspase-1 (1:1,000, Abcam, Cambridge, UK), IL-1 β (1:2,000, Abcam), and IL-18 (1:2,000, Abcam) at 4°C overnight. Then, membranes were incubated with HRP-linked secondary antibody (1:4,000, Abcam) for 1 hour at room temperature. The protein bands were displayed by using ECL kit (Beyotime Haimen, Jiangsu, China). Relative expression of the proteins was normalized to β -actin.

Immunohistochemistry Analysis

The sections of hippocampus tissues from each mouse were orderly incubated with 5% BSA blocking buffer for 30 minutes at 37°C, rabbit polyclonal antibody against NeuN (1:500, Abcam) and mouse monoclonal antibody against NLRP1 (1:500, Abcam) at 4°C overnight, and FITC-labeled anti-mouse IgG (1:200, Invitrogen) and TRITC-labeled anti-rabbit IgG (1:200, Invitrogen) for 1 hour at 37°C in the dark. Finally, the images were obtained using a Leica confocal microscope (Leica Microsystems, Wetzlar, Germany).

Cell Culture and Treatment

The human neuroblastoma cell line SH-SY5Y was purchased from American Type Culture Collection (ATCC). All cells were cultured in DMEM (Invitrogen, Grand Island, NY) supplemented with 10% FBS (Invitrogen), 1% penicillin, and 1% streptomycin at 37°C in an incubator with 5% CO_2 . The cells were divided into three groups: control group, $A\beta_{1-42}$ group, and $A\beta_{1-42}$ +SCH group. The cells in the $A\beta_{1-42}$ group were treated with 10 μ mol/L $A\beta_{1-42}$ (Sigma Company, Ltd, Beijing, China) for 24 hours. The cells in the $A\beta_{1-42}$ +SCH group were co-treated with 10 μ mol/L $A\beta_{1-42}$ and 10 μ mol/L SCH for 24 hours.

Statistical Analysis

All statistical analyses were implemented by using SPSS17.0 statistics software (SPSS, Inc., Chicago, IL,

USA), and the data are shown as mean±SD. The values of *P* lower than 0.05 were recorded as a significant difference. Comparisons between groups were analyzed by one-way analysis of variance (ANOVA).

Results

SCH Attenuated the Learning and Memory Impairments in AD Mice

Here, all mice were accepted MWM test at 2 weeks later for SCH treatment. Our data shows that AD mice spent more time in escape latency compared with normal mice. Nevertheless, SCH treatment could obviously shorten the escape latency time in AD mice (Figure 1A). Compared with normal mice, AD mice move a longer path length to find the escape platform, while the length can be obviously declined by SCH treatment (Figure 1B). Compared with normal mice, AD mice spent less time in the target quadrant, while SCH treatment could increase the residence time (Figure 1C). Furthermore, the time of AD mice crossing the platform was significantly less than normal mice. SCH treatment also significantly increased the time of crossing the platform in AD mice (Figure 1D). According to the results of MWM test, SCH effectively improved the cognitive impairment in AD mice.

Furthermore, we found that the production of A β ₁₋₄₂ and A β ₁₋₄₀ in the brains of AD mice were promoted, while SCH treatment could markedly reduce the production of them (Figure 1E and F).

SCH Repressed Neuronal Apoptosis and Pyroptosis in AD Mice

Subsequently, to explore the effect of SCH on neuronal death in AD mice, the following experiments were implemented. Firstly, a higher apoptosis rate of neurons was found in the hippocampus of AD mice compared with normal mice, but the rate can be significantly downregulated by SCH treatment (Supplementary Figure 1 and Figure 2A). Next, we proved that the expression of pyroptosis-related proteins, including NLRP1, ACS, cleaved caspase-1, IL-1 β , and IL-18, were upregulated in the hippocampus of AD mice, while SCH treatment could effectively reduce the expression of these factors (Figure 2B and C). Moreover, the results of immunohistochemistry indicated that NLRP1 inflammasomes were obviously activated in the hippocampus neuron of AD mice, and SCH treatment could inactivate the NLRP1 inflammasome (Supplementary Figure 2 and Figure 3A). In addition, the production of IL-1 β and IL-18 was enhanced in AD mice, while it was downregulated by SCH treatment (Figure 3B

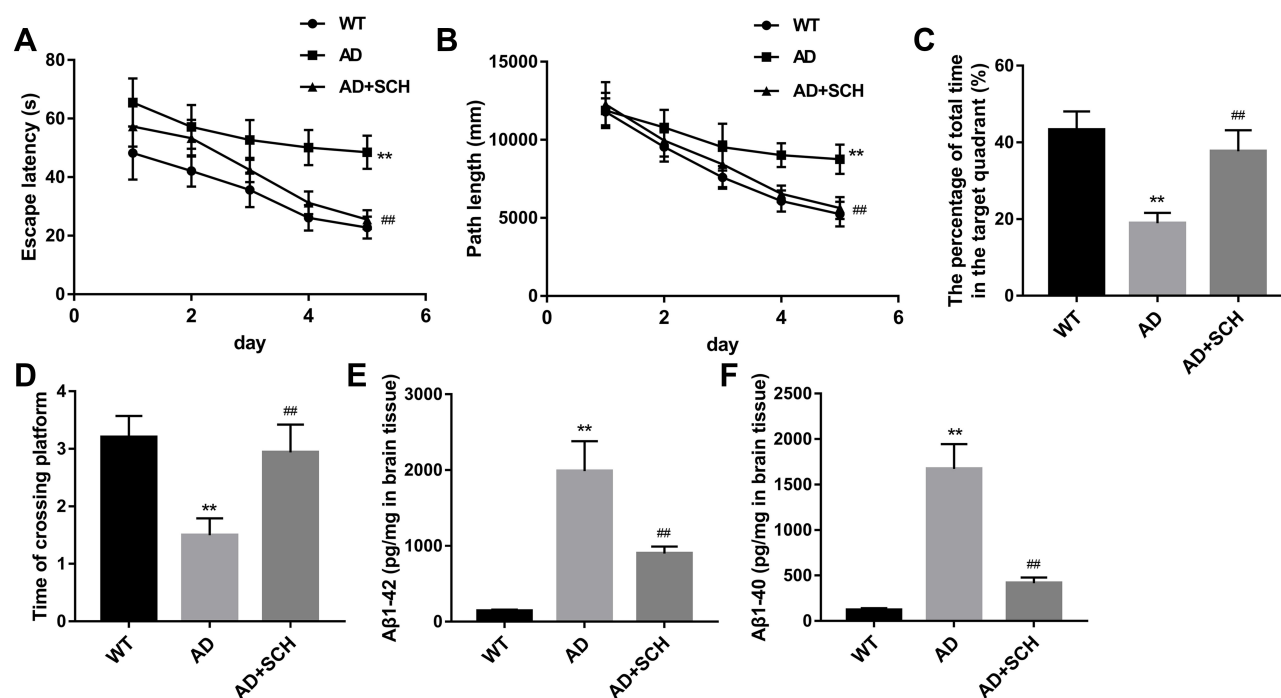


Figure 1 SCH enhanced the learning and memory functions in AD mice, and repressed the production of A β . The escape latency (A), path length (B), total time in the target quadrant (C), and crossing platform time (D) of mice were analyzed. (E and F) ELISA assay was performed to detect the production of A β ₁₋₄₂ and A β ₁₋₄₀ in brains of mice. ***P*<0.01 contrasted with the WT group, and ###*P*<0.01 compared with the AD group.

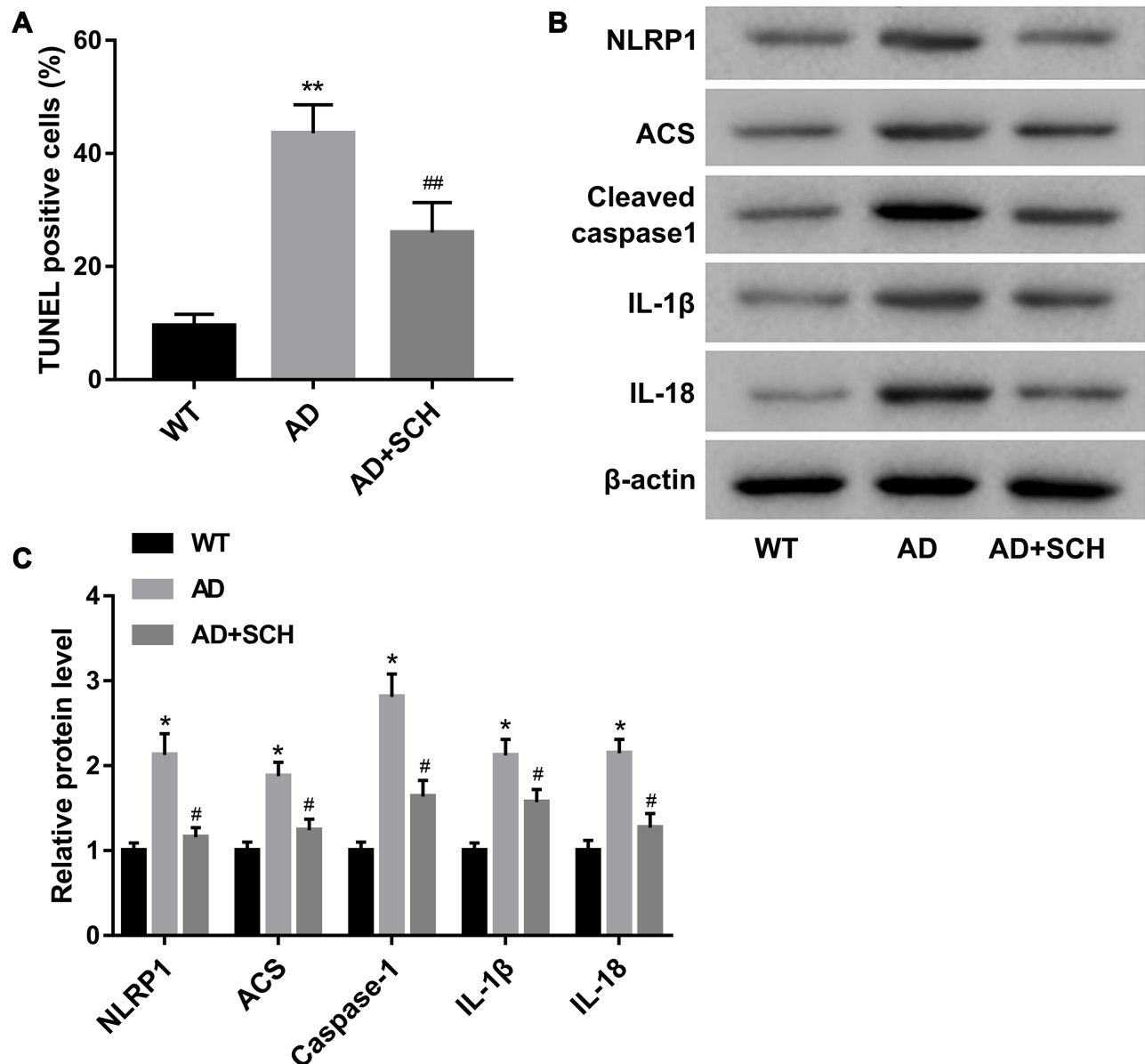


Figure 2 SCH repressed neuronal apoptosis and expression of pyroptosis-related proteins in the hippocampus of AD mice. **(A)** Apoptosis rate of neuron in CA1 region of hippocampus in each mouse was examined using TUNEL assay, and the percentage of TUNEL-positive cells was analyzed. **(B and C)** Expression of pyroptosis-related proteins, including NLRP1, ACS, cleaved caspase-1, IL-1 β , and IL-18, were examined using Western blot. Both * $P < 0.05$ and ** $P < 0.01$ compared with the WT group, and both # $P < 0.05$ and ### $P < 0.01$ compared with the AD group.

and C). In summary, AD-induced neuronal apoptosis and pyroptosis were improved by SCH treatment.

SCH Inhibited A β_{1-42} -Induced Neuronal Pyroptosis and Apoptosis

Next, we further verified the role of SCH in neuronal pyroptosis in vitro. Our data shows that A β_{1-42} -induced neuronal apoptosis were reversed by SCH treatment (Supplementary Figure 3 and Figure 4A). Furthermore, the expression of pro-apoptosis factors, caspase-3 and

Bax, were increased in A β_{1-42} -stimulated neuron, and anti-apoptosis factor, Bcl-2, was decreased. SCH treatment could obviously repress the expression of caspase-3 and Bax, and facilitate Bcl-2 expression (Figure 4B and D). In addition, highly expressed pyroptosis-related factors including NLRP1, ACS, cleaved caspase-1, IL-1 β , and IL-18, in A β_{1-42} -stimulated SH-SY5Y cells were reduced by SCH treatment (Figure 4C and E). IL-1 β and IL-18 production levels in the cell culture medium of A β_{1-42} -treated SH-SY5Y cells were increased, while then they were declined by SCH treatment (Figure 4F and G).

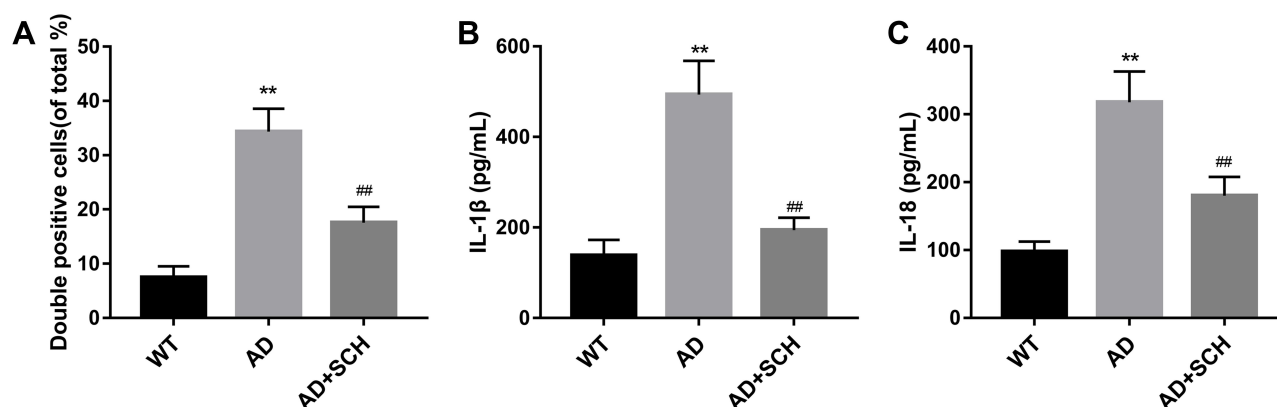


Figure 3 SCH inhibited the activation of NLRP1 inflammasome in hippocampus neuron of AD mice. (A) Immunohistochemistry was carried out to detect the activation of NLRP1 inflammasome in hippocampus neurons of each mouse, and the percentage of NLRP1-positive neurons was analyzed. (B and C) ELISA assay was implemented to measure the production of IL-1 β and IL-18 in the hippocampus of each mouse. ** $P < 0.01$ contrasted with the WT group, and ## $P < 0.01$ compared with the AD group.

Overall, our data revealed that A β_{1-42} -induced neuronal pyroptosis and subsequent apoptosis were repressed by SCH.

Discussion

APP/PS1 double transgenic mice express both APP and PS1, which are two genes closely associated with AD. Mutation of APP can result in excessive production of A β in mice brain, and mutation of PS1 can accelerate the formation of amyloid plaques.¹⁹ It was demonstrated that obviously amyloid plaques can be found in the brains of APP/PS1 double transgenic mice when 4-months-old, and cognitive impairment occurred in 12-month-old mice.²⁰ Hence, APP/PS1 double transgenic mice is widely regarded as an AD mouse model. In this present study, APP/PS1 double transgenic mice were used for the animal experiments.

It was evaluated that about 50 million people affected by AD globally, and the prevalence may be up to 100 million by 2050.²¹ Currently, the pharmacotherapy of AD focuses mainly on cholinergic and glutamatergic systems impairment. Donepezil, rivastigmine, and galantamine are the important drugs for AD treatment. However, existing drugs are only symptomatic but do not modify the disease.²² In recent years, the excellent therapeutic effect of TCM in many disorders was gradually accepted by the world, such as salvia miltiorrhizae was used against acute myocardial infarction, guanxinjing capsule was used to against coronary heart disease, and Danggui Shaoyao San was used against AD.^{23–25} Here, we clarified the regulatory mechanism of SCH in AD. SCH is a mainly active

constituent of *S. chinensis*. The protective effect of SCH on multiple disorders has been reported in many studies.¹⁷ Wei et al¹⁸ indicated that SCH could obviously improve the cognitive impairment in APP/PS1 double transgenic mice, and reduce the deposition of A β . Moreover, Zhao et al²⁶ revealed that SCH protects against A β_{1-42} -induced downregulation of cell viability in SH-SY5Y cells through activation of PI3K/AKT signaling. Song et al²⁷ indicated that SCH could effectively attenuate the neuroinflammation and cognitive deficits in an streptozotocin-induced AD rat model via inactivation of NF- κ B signaling. However, the action mechanism of SCH in AD development remains not fully clear. Here, we also found that SCH notably improved the learning and memory functions in AD mice. SCH declined the production of A β in brains of AD mice. In addition, we further indicated that SCH repressed the neuronal apoptosis in brains of AD mice as well as A β -induced SH-SY5Y cells.

Loss of neurons resulting from neuronal apoptosis is a crucial pathological feature of AD, related to a complex molecular mechanism. In recent studies, overwhelming numbers of studies have proved that pyroptosis, an inflammatory form cell death program, plays an important role in the development of AD.²⁸ Pyroptosis mainly consists of NLRP1, ACS, IL-1 β , and IL-18. It was proved that A β -induced activation of NLRP3 inflammasomes could activate caspase 1, and then induce the production of IL-1 β and IL-18, finally leading to neuronal apoptosis in AD.²⁹ Tan et al¹⁰ found that the expression of cerebral NLRP1 is increased in APP/PS1

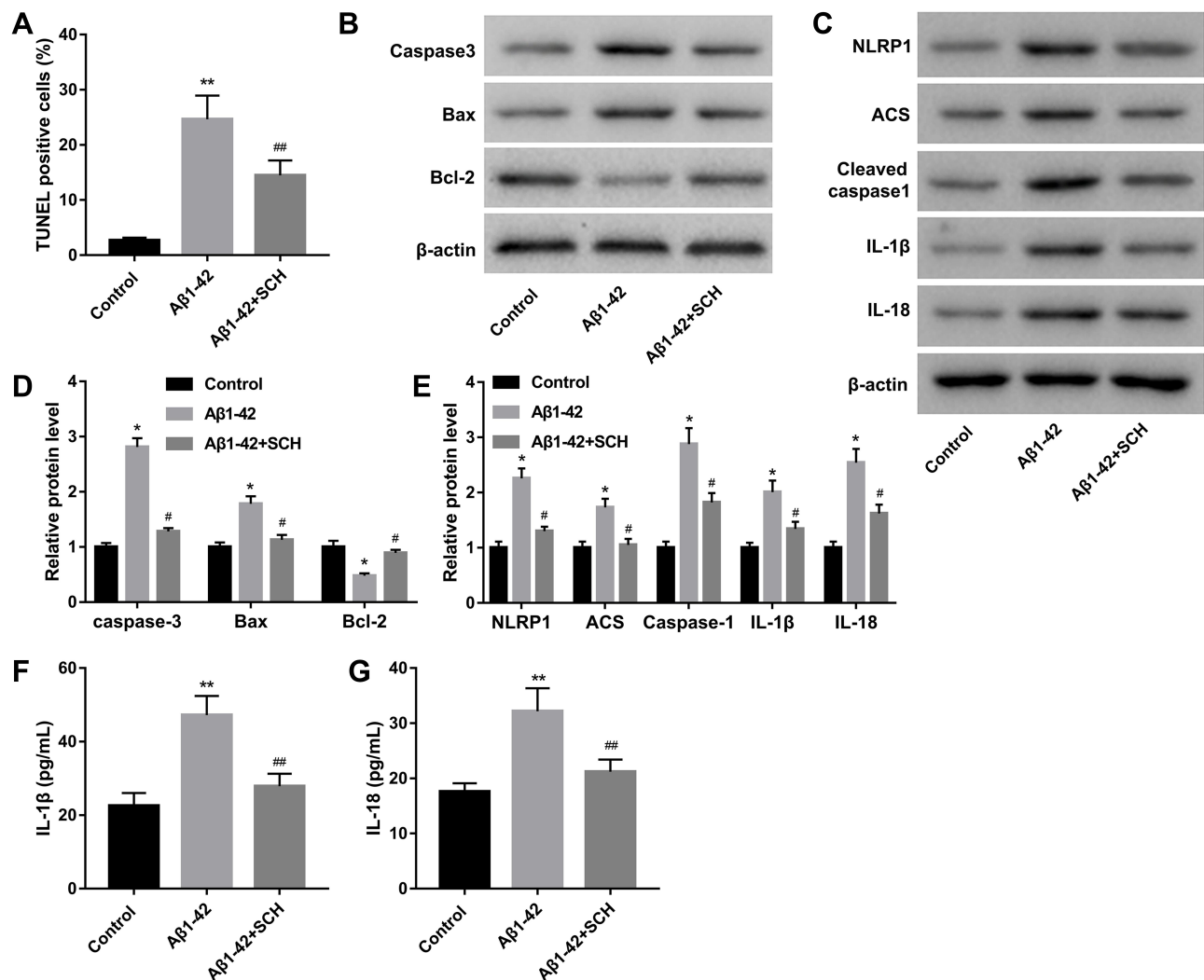


Figure 4 SCH repressed Aβ₁₋₄₂-induced neuronal apoptosis and pyroptosis. **(A)** Apoptosis rate of neuron was ensured by using TUNEL assay, and the percentage of TUNEL-positive cells was analyzed. **(B and D)** The expression of apoptosis-related proteins, including caspase-3, Bax, and Bcl-2, was detected by Western blot. **(C and E)** Western blot was performed to measure the expression of pyroptosis-related proteins in SH-SY5Y cells. **(F and G)** ELISA assay was carried out to examine the concentration of IL-1β and IL-18 in cell culture medium of SH-SY5Y. **P*<0.05 and ***P*<0.01 contrasted with the control group. ###*P*<0.01 and ##*P*<0.05 contrasted with the Aβ₁₋₄₂ group.

double transgenic mice. NLRP1-mediated caspase-1-dependent neuronal pyroptosis was obviously impeded by knockdown of NLRP1 and caspase-1. In our work, we found that SCH could notably repress the activation of NLRP1 inflammasome and neuronal pyroptosis both in AD mice and Aβ-induced SH-SY5Y cells.

Conclusion

Overall, our data demonstrated that SCH effectively improved the cognitive functions in AD mice through inhibition of NLRP1-mediated neuronal pyroptosis and neuronal apoptosis. Our data provided strong evidence to support SCH acting as a potential drug for AD treatment. Meanwhile, we indicated a novel protective mechanism of SCH in AD.

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Disclosure

The authors declare no conflicts of interest for this work.

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