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Original Article

Total Alkaloids of *Tripterygium wilfordii* Improve Alzheimer's Disease in Mice Through Antioxidation, Anti-Neuronal Apoptosis and Anti-Neuroinflammation

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ABSTRACT

Objectives: To explore the effect of total alkaloids of *Tripterygium wilfordii* (TAPC) on Alzheimer's Disease (AD) in mice through antioxidation, anti-neuronal apoptosis and anti-neuroinflammation. **Materials and Methods:** The experimental mice were divided into control (group A), model (group B) and total alkaloid treatment (group C) group. AD model was induced by D-galactose/ AlCl3. The group A was normal and healthy mice, the group B and A were given 160 mg/kg normal saline, and the AD mice in the group C were given 160 mg/kg total alkaloids. The behavior of mice in each group was compared and the cell morphology was detected by HE staining. The TNF-α, IL-1β, NF-κB and Cox-2 were detected by ELISA, and the expression levels of GSH-PX, CAT and SOD were detected by IHC. The apoptosis-related proteins and Caspase-3 was detected by Western blot. **Results:** The escape latency time of the group B was increased than group A, the crossing times of the target area and the stay time in the target area decreased, and the escape latency time decreased in the group C. The number of hippocampal nerve cells in the group B was decreased than group A, the arrangement was irregular, the tissue was loose, and a small number of cell bodies shrunk. Nuclear pyknosis and deep staining. The hippocampal neurons in the group C were arranged in an orderly and orderly manner, and the cells were no longer pyknotic, but the local tissue was still loose and tended to improve as a whole. The TNF-α, IL-1β, NF-κB and cox-2 in the group B were increased than group A, these in the group C were decreased than group B, while the e GSH-PX, CAT, SOD and MDA in the group B were reduced than group A, these in the group B were raised than group A. The Bax and Caspase-3 increased and the Bcl-2 decreased in the group B than group A, while these increased in the group C. **Conclusion:** The total alkaloids of TAPC have the potential to improve AD through the mechanisms of antioxidation, anti-neuronal apoptosis and anti-neuroinflammation.

Keywords: Total alkaloids of *Tripterygium wilfordii*, Alzheimer's disease, Antioxidation, Anti-Neuronal Apoptosis, Anti-Neuroinflammation.

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INTRODUCTION

Alzheimer's Disease (AD) is a chronic degenerative disease that affects the nervous system and its main symptoms include cognitive and memory decline.[1] The disease accounts for 60 to 80% of AD. According to data released by the International Alzheimer's Association, there are about 46.8 million patients worldwide, and that number is expected to double by 2030, with new patients likely to appear every 33 sec by 2050.[2] The disease seriously affects the quality of life. Although some progress has been made in the research on AD, its etiology and exact molecular mechanism are not fully understood, and clinical drugs still cannot effectively cure the disease. Synthetic drugs are one of the key means of treatment, which are mainly divided into two categories: acetylcholinesterase inhibitors and glutamate receptor antagonists.[3] More studies have focused on finding natural products in order to provide new ideas for the treatment of AD. Total alkaloids of *Tripterygium wilfordii* (TAPC) have significant antioxidant, anti-inflammatory and neuroprotective effects.[4] Previous studies have found that total alkaloids of TAPC can improve the learning and memory ability of AD model mice, and inhibit nerve cell apoptosis and neuroinflammation.[5] However, the specific molecular mechanism of total alkaloids of *Radix Rehmanniae* in improving AD has not been fully elucidated. In order to further study the effect of total alkaloids of TAPC on

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improving AD and its molecular mechanism, this study focused on the mouse model of AD. to explore the effect of total alkaloids of *Radix Scutellariae* on improving AD through antioxidation, anti-neuronal apoptosis and anti-neuroinflammation, and explain its possible mechanism, in order to provide new theoretical basis and research basis for the treatment of AD.

MATERIALS AND METHODS

Experimental animal

Eighteen SPF male mice, aged 13-15 weeks and weighing 18-22 g, were selected from Shanghai Shrek Experimental Animal Co., Ltd., license No. Wydw (Shanghai) 2014-0058. The room temperature is controlled at 22±2°C and the humidity is controlled at 60±10%. Adapt to the environment and keep for a week.

Experimental grouping

The mice were placed in the standard experimental environment (22±2°C, relative humidity 60±10%). After adapting to the environment, 6 mice were randomly selected as the control group (group A). The remaining 12 mice received intraperitoneal injection of D-galactose at the dose of daily 120 mg/Kg and intragastric administration of AlCl3 at the dose of daily 20 mg/Kg for 40 days to induce the mouse model of AD. The mice in the control group received the same amount of normal saline intraperitoneal injection and intragastric administration every day. The model mice were randomly divided into model (group B) and total alkaloid (group C) group, 6 mice in each group, group B and A were given 160 mg/kg normal saline, and total alkaloids of 160 mg/kg were given intragastric administration in group C.

Drugs, reagents and instruments

Total alkaloid of TAPC (manufacturer: Chengdu Munster Biotechnology Co., Ltd., item number: A0031. Dose: 20mg/branch), D-galactose (manufacturer: Shenzhen Jinfuyuan Biotechnology Co., Ltd.), AlCl3 (Jinan Dakui Chemical Co., Ltd.), ELISA kit (including TNF- α, IL-1β, NF-κB, cox-2 detection kit) (manufacturer: Thermo Fisher Scientific), immunohistochemical kit (including GSH, AchE, MAP2 detection kit) (manufacturer: Sigma-Aldrich), Westenblot instrument (Bax, Bcl-2, Caspase-3 detection reagent) (manufacturer: Bio-Rad).

Experimental scheme

Behavioral examination

Behavioral assessment was initiated on the 21st day after administration. The Morris water maze test was carried out in a circular pool with a diameter of 100 cm, a depth of 30 cm and a height of 50 cm. The pool was divided into four quadrants. The first quadrant was put into the 9 cm round table, and the 1 cm was under the surface of the water. The mice in the quadrant could not recognize the water temperature of the round table by adding appropriate amount of titanium dioxide to the pool and stirring until turbid. The tests covered adaptation to the water maze (day 1), positioning navigation skills test (days 2 to 5) and space exploration ability test (day 6). One day before the experiment, the rats were placed in the laboratory to adapt to the environment and reduce their fear. In the positioning navigation skill test, each mouse was tested four times a day, facing the pool wall and entering the water from the midpoints of four different quadrants. After finding the platform, the rats need to stay on it for 10 sec. If the mouse fails to find the underwater platform within 90 sec, the experimenter will guide it to the platform and stay for 10 sec. Record the swimming path of the mouse and the distance swam to the platform. The space exploration ability test is conducted on the 7th day, and the platform is removed at this time. The mice entered the water from the opposite side of the platform quadrant in the positioning navigation skill test, and recorded the swimming, the total swimming distance and the number of times passing through the target quadrant within 90 sec. Spatial learning and memory can be measured by the ratio of swimming distance to total distance in the 90s target quadrant and the number of times crossing the target quadrant.

H&E staining

After 12 hr of water maze experiment, the rats in the three groups were killed with guillotine, and the brain, hippocampal tissue and serum samples were taken immediately. Soak the tissue sections in xylene solution for 10 min, then change xylene for 10 min, then soak for 10 min, then use gradient ethanol hydration (100%, 95%, 90%, 80%), rinse with tap water, followed by hematoxylin staining, soak the hydrated slices in hematoxylin dye solution for 5-20 min, make the nucleus purple-blue, then rinse with tap water for 3-5 min. After being differentiated by 1% hydrochloric acid alcohol for 5-30 sec, rinse with tap water for 1-3 min; then return to blue for 30 sec-1 min with weakly alkaline aqueous solution and rinse fully with tap water for 5-10 min; then perform eosin staining, put the fully hydrated slices directly into the eosin staining solution, dye the cytoplasm pink for about 5-15 min, and then perform gradient ethanol dehydration (90%, 95%, 100%). Finally, transparent slices were made with xylene solution, and finally sealed with neutral gum.

ELISA

Blood samples were collected after each group of mice were killed. The blood was placed at room temperature for static coagulation, then at 4°C, the serum was collected after centrifugation after 3000r stop mineling for 10 min. The enzyme labeling instrument was preheated to 37°C. The standard samples were diluted according to the dilution ratio provided in the experimental manual. The serum sample to be tested was added to the sample diluent 40 μL, and then added to the enzyme plate. Put the enzyme plate into the enzyme meter and incubate according to the recommended time in the experimental manual. Wash the enzyme plate with detergent, then pat dry. The substrate solution

was added and incubated in an enzyme-labeled instrument. The chromogenic agent was added and then incubated in the enzyme labeling instrument. The terminating solution was added, and then the absorbance of each hole was determined by enzyme labeling instrument. According to the experimental results, the TNF- α, IL-1 β, NF- κ B and cox-2 in serum of mice in each group were calculated.

Immunohistochemistry

After dewaxing and hydration of paraffin slices, rinse 3 times / 3 min with PBS (pH7.4). According to the antibody instructions, the mouse tissues were repaired with appropriate antigens. The activity of endogenous catalase was blocked by hydrogen peroxide blocking solution and placed at room temperature for 10 min. Then rinse 3 times / 3 min with PBS, and use 50 μL normal non-immune animal serum. Remove the blocking solution, add 50 μL normal non-immune animal serum to each slice and leave it at room temperature for 10 min. Then remove the serum, add an antibody to each section and spend the night at 4°C. Rinse again with PBS for 3 times / 3 min. Then the second antibody labeled with biotin and Streptomyces avidin-peroxidase solvent were added and 10min was placed at room temperature. Finally, rinse 3 times / 3 min with PBS. Each slice was stained with freshly prepared DAB solution, and 3-10 min was observed under microscope. Then rinse with tap water, re-dye hematoxylin, rinse again, and finally return to blue. After gradient alcohol dehydration and drying, (xylene transparent) and neutral gum sealing, the slices are completed.

Western blot

50 mg was extracted from brain tissue, and Ripa 200 μL lysate was added to the lysate to fully lyse the cells. The protein was quantified according to the working solution prepared according to BCA kit. The supernatant was separated by SDS and transferred to PVDF membrane. An amount of 10 m1 5% skimmed milk powder was sealed and incubated overnight at 4°C for 2 hr or at room temperature for 2 hr. After the PVDF membrane was incubated in an anti-RhoA treatment at 4°C, TBST washed off the first antibody that binds to the membrane, and a second antibody was added and incubated at room temperature for 2 hr for 1 hr. ECL chemiluminescence was used for coloration.

Statistical method

The data were statistically analyzed by SPSS20.0, and the measurement data were expressed by x±s. Independent sample t-test was used for comparison. The difference was statistically significant ($p<0.05$). Compared with the group A, $^{a}p<0.05$; compared with the group B, $^{b}p<0.05$

RESULTS

Effects of total alkaloids of TAPC on mice behavior

The escape latency time of the group B was increased, the crossing times of the target area and the stay time in the target area decreased than group A, while the escape latency time of the group C decreased compared with the group B (Table 1 and Figure 1).

Cell morphology was examined by HE staining in three groups

The number of hippocampal nerve cells in the group B decreased, the arrangement was irregular, the tissue was loose, and a small number of cell bodies shrunk than group A. Nuclear pyknosis and deep staining. The hippocampal nerve cells in the group C were arranged in an orderly and orderly manner, and the cells were no longer pyknotic, but the local tissue was still loose and the whole tended to improve than group B (Figure 2).

The Inflammatory factor levels

Compared with the group A, the TNF-α, IL-1β, NF-κB and cox-2 in the group B were increased, while these in the group C were reduced than group B (Table 2 and Figure 3).

The GSH-PX, CAT, SOD and MDA level

The GSH-PX, CAT and SOD in the group B were decreased, while the MDA was increased than group A. The GSH-PX, CAT and SOD in the group C were increased, while the MDA was decreased in the group B (Table 3 and Figure 4).

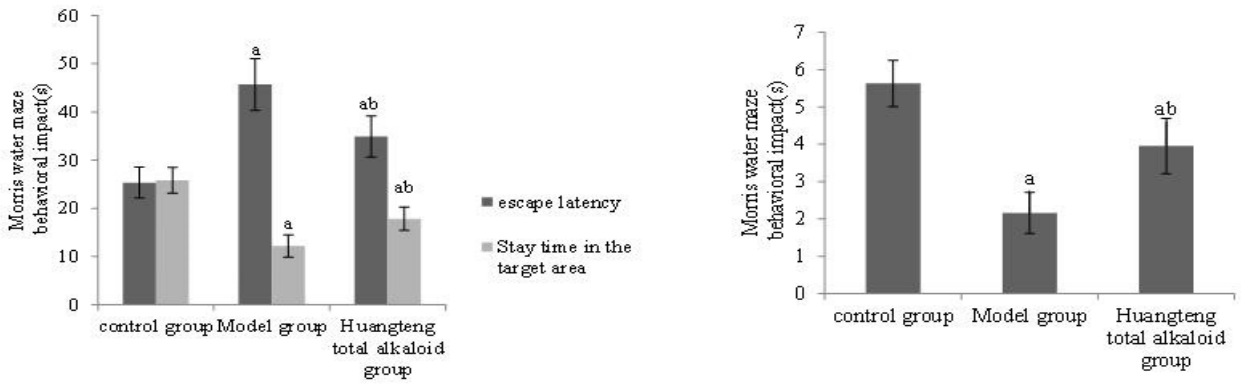

Figure 1: Effects of total alkaloids from Huangteng on Morris water maze behavior in mice.

Table 1: Effects of total alkaloids of TAPC on behavior of Morris water maze in mice ($\bar{x}$±s, *n*=6).

Group	Escape incubation period (s)	Number of times to cross the target area (times)	Target area residence time (s)
A	25.36±3.21	5.63±0.62	25.85±2.69
B	45.69±5.33 [a]	2.16±0.55 [a]	12.16±2.31 [a]
C	34.91±4.25[ab]	3.96±0.74 [ab]	17.85±2.41 [ab]
F	32.8	43.91	46.32
P	<0.001	<0.001	<0.001

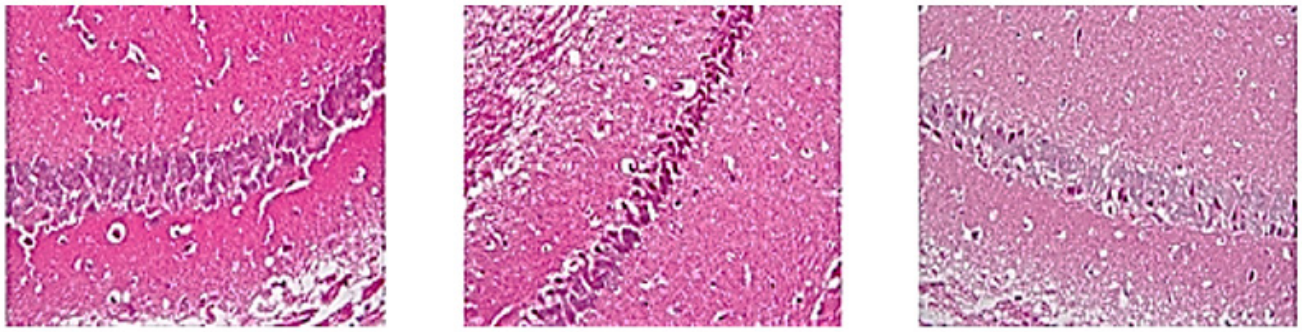

Figure 2: Cell morphology of animal brain tissue sections stained with HE.

The expression apoptotic protein

The Bax and Caspase-3 increased and the Bcl-2 decreased in the group B than group A, while the Bax and Caspase-3 decreased and the Bcl-2 increased in the group C compared with the group B (Table 4 and Figure 5).

DISCUSSION

AD is a degenerative disease of the central nervous system[6] Among its pathological features are Senile Plaque (SP), formed by deposition of beta-amyloid peptide, and loss of neurons in the cerebral cortex and hippocampus,[7] At present, there is no specific therapeutic drug. Therefore, it is of great significance to find drugs with significant anti-AD. Fibraurea recisa Pierre, taken from the genus Tripterygium of the family Tripterygium, is a dry vine with bitter taste and cold, with the effect of clearing away heat and detoxification, purging fire and defecating. It is mentioned for the first time in Compendium of Materia Medica and is included in the 2015 edition of Chinese Pharmacopoeia. Previous studies have found that total alkaloids of TAPC have a variety of pharmacological effects, such as anti-tumor, anti-osteoarthritis, antiviral, neuroprotective, antidepressant and reducing blood lipids, but its mechanism in AD is not clear.

TNF-α and IL-1β are two main inflammatory cytokines in the inflammatory process. The release of TNF-α and IL-1β may lead to neuronal damage and aggravation of inflammatory response, thus promoting the development of AD. TNF-α and IL-1β can activate astrocytes and microglia and increase the release of other pro-inflammatory factors. Xia Jing *et al.*,[8] found that reducing the expression of TNF- α and IL-1 β inflammatory factors can effectively improve the overall cognitive function, daily behavior and mental behavior of the elderly. Di Tingting *et al.*,[8] found that the massive release of NF-κB can lead to a large number of neuronal damage in the brain of mice. Cox-2 is an enzyme associated with inflammation and pain sensation that catalyzes the synthesis of peanut acid into prostaglandins during inflammation. Cox-2 is involved in the neuroinflammatory response of AD and may play a role in neuronal damage. In this study, ELISA was used to detect the TNF- α, IL-1 β, NF- κ B and cox-2. The results showed that the TNF-α, IL-1β, NF-κB and cox-2 in the group B were raised than group A, while these in the group C were decreased than group B. It is suggested that total alkaloids of TAPC can effectively reduce the TNF-α, IL-1β, NF-κB and cox-2 inflammatory factors and alleviate the inflammation of AD induced by D-galactose/AlCl3.

In this study, ELISA was used to detect the TNF-α, IL-1β, NF-κB and cox-2. The results showed that these in the group B were higher than group A, while these in the group C were lower than group B. It is suggested that total alkaloids of TAPC can effectively reduce the TNF-α, IL-1β, NF-κB and cox-2 inflammatory factors and alleviate the inflammation of AD induced by D-galactose/AlCl3. Yang Yixin *et al.*,[9] found that it inhibited the expression of MDA, upregulated the SOD and GSH-PX, and improved the learning and memory ability of mice. In this study, the GSH-PX, CAT and SOD were detected by immunohistochemical method, and the results showed that compared with the control group, the GSH-PX, CAT and SOD in the group B were lower than group A, while the MDA in the group B were increased than group B. Compared with the group B, the GSH-PX, CAT, SOD and MDA in the group C were higher than group B. It is suggested that the total alkaloids of TAPC can help to remove harmful free radicals and peroxides, protect neurons and brain cells from oxidative damage, reduce nerve cell death, and improve the symptoms and prognosis of patients.

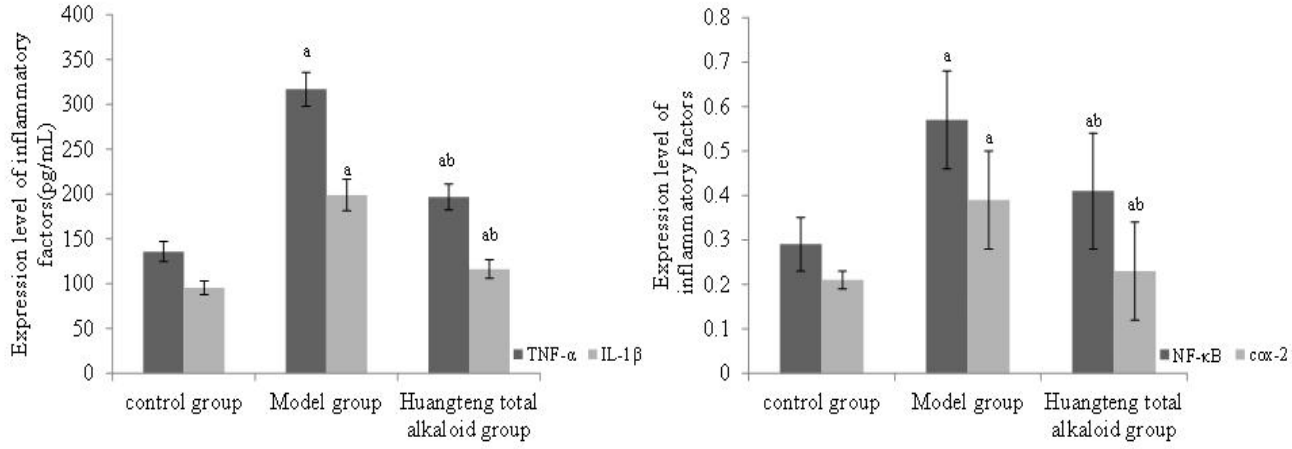

Figure 3: Comparison of three groups of inflammatory factor level.

Table 2: The inflammatory factor levels ($\bar{x}$±s, *n*=6).

Group	TNF-α (pg/mL)	IL-1β (pg/mL)	NF-κB	cox-2
A	135.86±11.27	95.33±7.62	0.29±0.06	0.21±0.02
B	316.83±18.85 [a]	198.86±17.57 [a]	0.57±0.11 [a]	0.39±0.11 [a]
C	196.74±14.36 [ab]	116.33±10.36 [ab]	0.41±0.13 [ab]	0.23±0.11 [ab]
F	269.6	113.71	10.9	7.12
P	<0.001	<0.001	<0.001	0.006

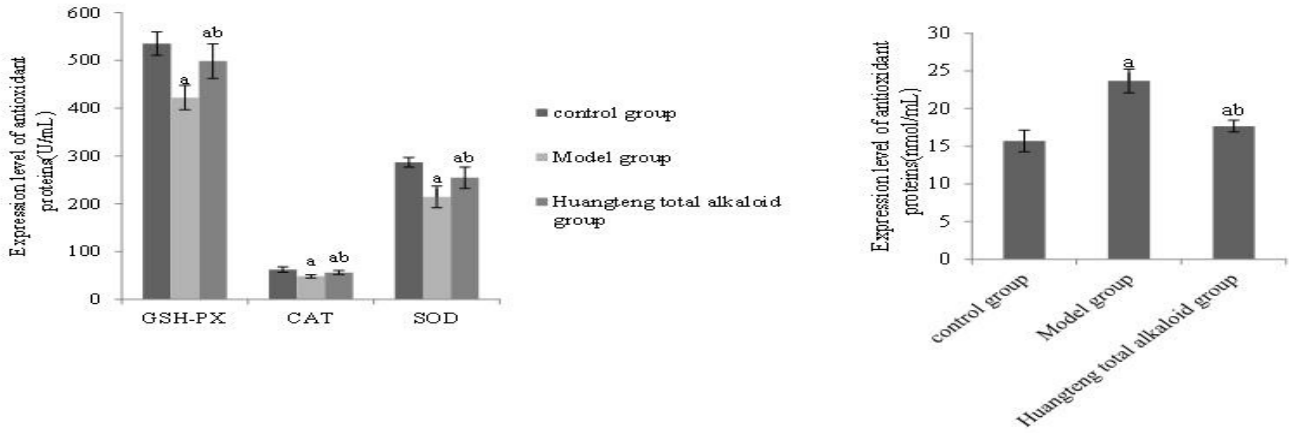

Figure 4: Comparison of expression levels of GSH-PX, CAT, SOD, and MDA among three groups.

Bax is a protein that promotes apoptosis, and its expression and activity are up-regulated in neurons of AD patients.[10] Bcl-2 protein is the coding product of Bcl-2 proto-oncogene and an anti-apoptotic protein. It can prevent the activation of Bax and keep cells alive. Apoptosis depends on Bcl-2/Bax ratio.[11] Caspase-3 is an important apoptotic executive protein, which plays an important role in neuronal apoptosis. In the hippocampus of patients with AD, the activity of Caspase-3 is increased, suggesting that neuronal apoptosis may be related to this enzyme.[12,13] found that it decreased the Bax, Bcl-2 and Caspase-3, promoted the production of anti-apoptotic protein Bcl-2, and improved the learning and memory impairment caused by Aβ. In this study, the Bax, Bcl-2 and Caspase-3 were detected by Western blot method. The results showed that the Bax and Caspase-3 in the group B increased than group A, while the Bcl-2 decreased. The Bax and Caspase-3 in the group C were decreased than group A, and the Bcl-2 was increased. It is suggested that total alkaloids of TAPC can reduce the expression of Bax and Caspase-3 in the brain of AD mice, increase the activity of Bcl-2, and inhibit the apoptosis of brain tissue of AD mice. However, how the total flavonoids exert a specific effect is still unclear. Studies have found that fibrauretin, the effective component of total flavonoids, relies on the PI3K/Akt/GSK-3β signal transduction pathway to significantly improve AD symptoms caused by Aβ1-42. Its antioxidant, anti-inflammatory and anti-apoptosis effects,[14] and whether other pathways are involved also needs to be further improved.

Table 3: The GSH-PX, CAT, SOD and MDA levels ($\bar{x}\pm s$, $n=6$).

Group	GSH-PX (u/mL)	CAT (u/mL)	SOD (u/mL)	MDA (nmol/mL)
A	535.29±24.69	62.33±5.56	286.69±10.26	15.69±1.44
B	422.36±25.63 [a]	48.29±3.63 [a]	214.59±22.63 [a]	23.67±1.58 [a]
C	498.37±36.21 [ab]	56.33±4.26 [ab]	254.38±22.52 [ab]	17.66±0.79 [ab]
F	23.15	14.35	20.88	59.88
P	<0.001	<0.001	<0.001	<0.001

Table 4: The expression levels of apoptotic protein in 3 groups were compared ($\bar{x}\pm s$, $n=6$).

Group	Bax	Bcl-2	Caspase-3
A	1.00±0.13	1.00±0.07	1.00±0.07
B	1.59±0.16 [a]	0.66±0.07 [a]	1.61±0.11 [a]
C	1.09±0.13 [ab]	0.96±0.06 [ab]	1.13±0.32 [ab]
F	30.62	46.39	63.86
P	<0.001	<0.001	<0.001

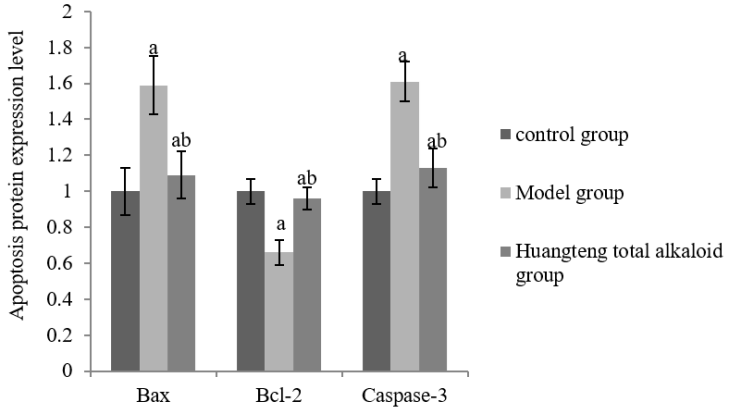

Figure 5: Comparison of expression levels of Bax, Bcl-2, and Caspase-3 in three groups.

CONCLUSION

To sum up, the total alkaloids of TAPC can increase the activities of GSH-PX, CAT and SOD, realize antioxidant stress, significantly reduce the inflammatory factors, inhibit the Bax and Caspase-3, increase the Bcl-2, and inhibit neuronal apoptosis.

ACKNOWLEDGEMENT

We would like to express our sincere gratitude to all those who have contributed to the completion of this study.

ABBREVIATIONS

TAPC: Tripterygium wilfordii; **AD:** Alzheimer's disease; **SP:** Senile plaque.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Has received research ethics approval from the People's Hospital of Yubei District of Chongqing.

SUMMARY

The article investigates the effects of total alkaloids from *Tripterygium wilfordii* (TAPC) on Alzheimer's Disease (AD) in mice. The study aimed to explore the antioxidative, anti-apoptotic, and anti-inflammatory properties of TAPC as potential therapeutic mechanisms. Experimental groups included a control group, a model group induced with AD, and a treatment group receiving TAPC. The results showed that TAPC significantly improved behavioral outcomes, reduced inflammation markers (TNF-α, IL-1β, NF-κB, and Cox-2), enhanced antioxidative enzymes (GSH-PX, CAT, SOD), and inhibited neuronal apoptosis by regulating apoptotic proteins (Bax, Bcl-2, Caspase-3). These findings suggest that TAPC could be a promising therapeutic

agent for AD by targeting oxidative stress, inflammation, and apoptosis.

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