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Effect of Danlou Tablet on the Expression of β-Amyloid and Inflammatory Factors in the Brain of SAMP8 Mice

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Abstract

Purpose: Alzheimer's disease is a neurodegenerative disease characterized by β-amyloid protein deposition and neuroinflammatory response. The aim of this study was to investigate the effects of Danlou tablet on β-amyloid metabolism and inflammatory factor expression in the brain of SAMP8 Mice.

Methods: 18 rapidly aging mice (SAMP8) were used as Alzheimer's disease model mice, and 6 normally aging SAMR1 mice were used as control groups. SAMP8 mice were divided into: control group, Danlou tablet drug group and positive control drug group. The positive control drug was the drug donepezil hydrochloride, which was given by gavage. Immunohistochemistry and Western blot were used to determine the expression of brain

Aβ, APP, VCAM-1, MIP-1β, CCR5 in mice after gavage.

Results: Compared with the control group, levels of Aβ deposition in the brain of the mice in the Danlou tablet treatment group decreased. After the intervention with the Danlou tablet, the expression of VCAM-1, MIP-1β, CCR5 and other inflammatory factors in the brains of SAMP8 mice was significantly reduced.

Conclusion: Danlou tablet can inhibit Aβ deposition and neuroinflammatory response in the brain of SAMP8 mice, and may have important significance for the early prevention and treatment of Alzheimer's disease.

Keywords: Aβ; Alzheimer's disease; Neuroinflammation; Danlou tablet

Introduction

Alzheimer's disease is an irreversible neurodegenerative disease with progressive development. The pathogenesis of AD has not been fully elucidated. Its main pathological features are senile plaques formed by β-amyloid deposits, neurofibrillary tangles, a chronic inflammatory response of glial cell activation and proliferation, abnormal synaptic function and loss, neuronal degeneration and death, and more **[1,2].** In the surrounding tissues where Aβ is deposited, there is an obvious inflammatory response. Many studies have shown that the deposition of cerebral microvascular Aβ in AD patients promotes the occurrence of neuroinflammation **[3].** Another feature in the brain of AD patients is activated microglia and astrocytes, which release pro-inflammatory cytokines and chemokines. These adhesion molecules and chemokines participate in the neuroinflammatory cascade **[4,5].** In the brains of AD patients, the presence of inflammatory mediators and the increased expression of the complement cascade near Aβ deposition strongly indicate the role of inflammation in the pathogenesis of AD. This complex pathway network is mainly induced by adhesion molecules and cell chemotactic mediators. Here, we observed the expression levels of inflammatory mediators in SAMP8 mice. In recent years, the research of traditional Chinese medicine in the prevention and treatment of neurodegenerative diseases has been increasing. Danlou tablet is a national-level new Chinese medicine developed by Lei Zhongyi, a master of Chinese medicine, based on the Gualouxiebaibaijiu decoction in "The Synopsis of the Golden Chamber". It has the effects of promoting blood circulation and removing blood stasis, resolving phlegm and dispelling congestion. Danlou tablets are composed of Gualou peel, Xiebai, Danshen, Chuanxiong and other traditional Chinese medicines. Pharmacological studies have shown that the Danlou tablet can reduce the content of Nitric Oxide Synthase (NOS) in the serum of hyperlipidemia rats, protect the vascular endothelium, and improve Blood flow function, and has a better preventive effect on atherosclerosis **[6].** Its monomer components gallic acid, paeoniflorin, tanshinone IIA can reduce the inflammation of the central

nervous system [7]. In previous studies, it was found that the serum containing Danlou tablet can increase the cell activity after $A\beta_{1-40}$ induced BMEC injury and reduce the release of cellular lactate dehydrogenase [8]. This study aimed to investigate the effects of Danlou tablet on Aβ deposition and on the neuroinflammatory response in the brains of rapid aging model mice (SAMP8). The SAM model was bred from the AKR/J group in the early 1970s by Takeda and others of Kyoto University. The SAM subline is called the accelerated aging mouse susceptible 8 strain. It exhibits early learning and memory impairment, so it is often used to study aging and age-related diseases. It is characterized by early rapid aging accompanied by significant learning and memory impairment, and it will aggravate with age [9]. These mice show age-related Aβ overproduction. Therefore, these animals are considered to be models for studying the early pathology of AD. We examined the effects of Danlou tablet on the inflammatory response in the brain of SAMP8 mice by detecting the expression of Aβ and inflammatory mediators.

Experimental

Animals

The weight of 18 male SAMP8 mice and 6 SAMR1 mice were about 25.0 g, purchased from the first affiliated Hospital of Tianjin University of traditional Chinese Medicine. License number: SCXK (Jin) 2015-0003. The animals are kept at a density of 6 per cage, and they have free access to food and water. The animals were randomly divided into wild type control group (SAMR1 mice), control group (SAMP8 mice), Danlou tablet group (SAMP8 mice treated with 0.675 g/kg/d Danlou tablet) and positive control group (donepezil hydrochloride, SAMP8 mice treated with 1.667 mg/kg donepezil hydrochloride). After two months of gavage, mice were anesthetized with 10% chloral hydrate and the heart was rinsed with 0.9% saline. Take out the brain and separate it in the midline. Remove the brain and separate at the midline. One hemibrain was fixed in phosphate-buffered 4% paraformaldehyde (pH 7.4) for 26 hours at 4°C for vibrato sectioning. The hippocampus and cortex were separated from the rest of the hemispheres, quickly frozen in liquid nitrogen, and stored in a refrigerator at -80°C for Western blot analysis. All animal studies were conducted according to the protocol approved by the Animal Care and Use Committee of Henan University of Traditional Chinese Medicine.

Reagents and chemicals

Aβ antibody, Vascular Cell Adhesion Molecule-1 (VCAM-1), anti-chemokine receptor 5 (CCR5) and isotype control antibody were purchased from abcam (Cambridge, UK). Anti-phosphorylation and total Extracellular Signal-Regulated Kinase (ERK) 1/2 and Immunoglobulin G (IgG) antibodies were purchased from Wuhan

Beverly Bioengineering Co., Ltd. (Beverly, Massachusetts). All other chemicals used were purchased from Sigma-Aldrich (St. Louis, Missouri). Danlou tablet, purchased from Jilin Cornell Pharmaceutical Co., Ltd., National Medicine Standard: Z20050244.

Immunochemistry

Put the PBS solution in the 24-well plate, cut off the olfactory bulb and the cerebellum behind the chevron. The tissue tray is laid on the bottom with an embedding machine. After cutting flat, fix the tissue on the tissue tray (the front of the brain is on the top and the back is on the bottom). Set the slice thickness to 20-30 um. Put about 10 brain slices in each hole, and store them in a refrigerator at 4°C after slicing. Select the desired part of the brain slices, place 3-5 sheets per well in a 24-well plate, rinse with PBS for 5 minutes to remove the embedding agent and preservatives. Aspirate the PBS, add 0.5% Triton (diluted in PBS), 37°C for 1 hour. Shake and wash with PBS for 5 min, 3 times. Add blocking solution 7% goat serum (diluted with PBS) and place in a shaker at room temperature for 1.5 hours. Discard the serum, directly add the primary antibody (diluted with 7% goat serum according to the antibody instructions), about 100-150 ul/well, incubate at 37°C for 1h and put it in the refrigerator at 4°C overnight. Remove the primary antibody and wash with PBS for 5 min, 3 times. Add fluorescent secondary antibody (diluted with PBS according to the instruction ratio) about 100-150 ul/well, after all steps, wrap it in tin foil to avoid light, place it on a shaker at room temperature for 2 hours. Wash with PBS for 5 min, 3 times. Add the ready-to-use DAPI solution, about 50 ul/well, place it on a shaker at room temperature for 7 minutes, wash with PBS for 5 minutes, 3 times. After completing the above steps, the dark light patch is placed in a fluorescence microscope for observation.

Western blot

In order to determine the expression levels of APP, VCAM-1, MIP-1β, CCR5, Erk1/2, and p-Erk1/2 in the brain, Western blot analysis was performed. The brain tissue of each group of mice was homogenized. After centrifugation, the protein tissue was extracted, and the BCA protein quantification kit was used for protein quantification. The protein was loaded on a 12% polyacrylamide gel and transferred to a polyvinylidene fluoride membrane for immunoblotting analysis. Using the brain homogenate of each group of mice, β-actin was used as an internal control, and the following IgG antibodies were used to detect the expression of inflammatory mediators and signal transduction components: VCAM-1 (1:2000), CCR5 (1:1000), as well as anti-phosphorylation and anti-Total ERK1/2 MAPK kinase (1:1000) and JNK MAPK kinase IgG (1:1000). As the secondary antibody, goat anti-rabbit or goat anti-mouse peroxidase-conjugated IgG antibody (both 1:5000) was used. Chemiluminescence enhancement fluid (catalog number NEL103E001EA; PerkinElmer, Inc., Waltham,

Massachusetts, USA) was used to detect the signal. Quantity One software version 4.62 (Bio-Rad Laboratories, Inc, Hercules, California, USA) was used for optical density analysis. In all immunoblotting studies, at least 6 animals were used and representative data is shown.

Statistics

All measurement data at room temperature are expressed as mean ± standard deviation (x ± s), and all data are from at least 3 independent experiments. GraphPad Prism8.0 statistical software was used for analysis. When the comparison between multiple groups was in accordance with the normal distribution and the variance was homogeneous, single-factor analysis of variance was used, and then the Student Newman-Keuls (SNK) multiple comparison test was performed. $P<0.05$ indicates that the difference is statistically significant, and $P<0.01$ indicates that the difference is very significant.

Results

Danlou tablet treatment reduced Aβ deposition in the brain of SAMP8 mice

The extracellular deposition of beta amyloid in the brain is a prominent pathological feature of AD. Aβ is Amyloid Precursor Protein (APP) derived from the hydrolysis of β- and γ secretases. The level of Aβ in the brain depends not only on the production rate of Aβ, but also on its clearance rate through various clearance pathways. More and more AD treatment strategies aim to promote the clearance of Aβ from the brain. The main purpose of this study is to evaluate how Danlou tablet treatment affects the Aβ content in the brain of SAMP8 mice. For these studies, we examined the expression of Aβ in the brains of each group of mice by immunohistochemical analysis using an Aβ antibody, and detected the expression of APP in the brain of each group of mice by Western blotting. In our study, compared with control mice, the total Aβ deposition and APP expression in the hippocampus of model mice increased significantly. Compared with SAMP8 control mice, the decrease in brain Aβ content was more obvious in the Danlou tablet treatment group **(Figure 1),** and APP expression was also reduced **(Figure 2).** These findings indicate that treatment with Danlou tablet in SAMP8 mice significantly affected Aβ deposition in the brain.

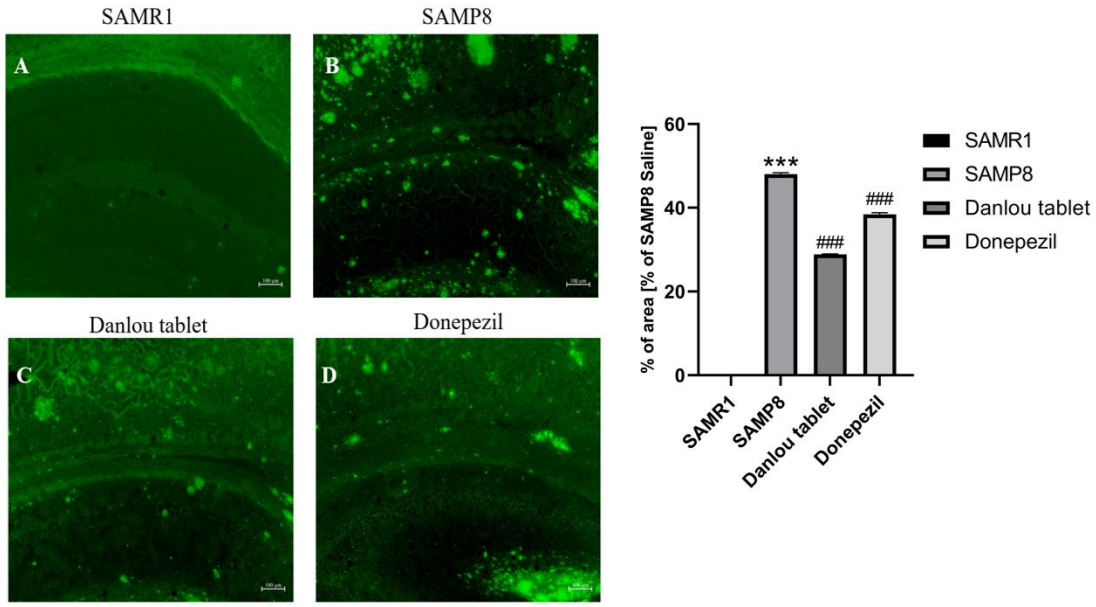

Figure 1: Aβ plaques in the hippocampus and cortex of each group of mice.

Compared with the **SAMR1** control group, *P<0.05, **P<0.01, ***P<0.001; compared with SAMP8 control group, #P<0.05, ##P<0.01, ###P<0.001 A: Aβ expression in SAMR1 mouse cerebral cortex B: Aβ expression in SAMP8 mouse cerebral cortex C: SAMP8 Aβ expression in cerebral cortex of mice after treatment with Danlou tablet D: Aβ expression in cerebral cortex of SAMP8 mice after treatment with Donepezil (scale bar=20 μm).

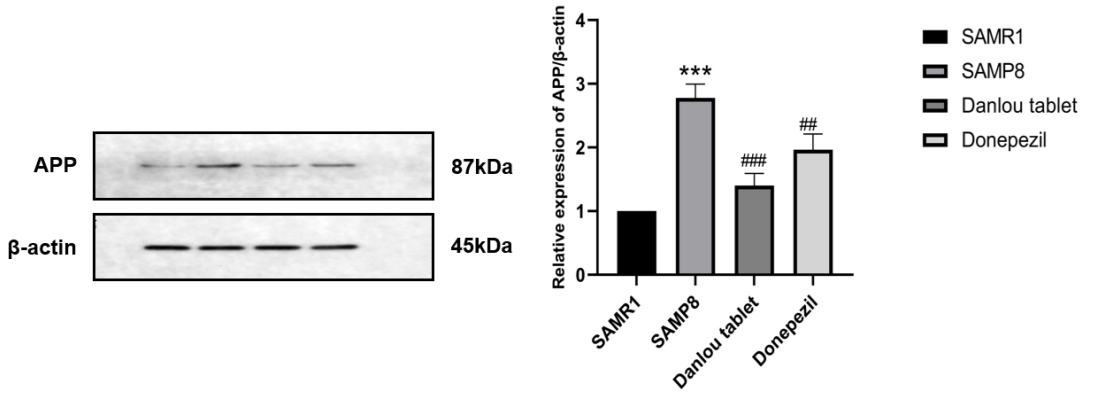

Figure 2: Expression of brain APP in each group.

Compared with normal control group, *P<0.05, **P<0.01, ***P<0.001; compared with model group, #P<0.05, ##P<0.01, ###P<0.001.

Danlou tablet treatment reduces the expression of inflammatory mediators VCAM-1, MIP-1β and CCR5 in the brains of SAMP8 mice

Previous studies have found that Aβ deposited in AD promotes the release of chemokines and adhesion molecules from endothelial cells. These factors destroy the blood-brain barrier, causing fibrinogen, immunoglobulin and white blood cells to enter the brain parenchyma, causing neuronal apoptosis, while simultaneously activating microglia and astrocytes, triggering a persistent neuroinflammatory response **[10].** In our study, the use of Western blotting showed that the expression of VCAM-1 protein in the model group was significantly increased, but this effect was weakened in the Danlou tablet treatment group **(Figure 3).** In addition, compared with control mice, the chemokine MIP-1β and its receptor CCR5 were significantly increased in model mice. However, we found that compared with SAMP8 mice, the expression of MIP-1β and CCR5 protein in the Danlou tablet treatment group was significantly reduced **(Figure 4).** In summary, these findings suggest that VCAM-1, MIP-1β and CCR5 are involved in the biological and pathological processes of AD, and the efficacy of Danlou tablet in improving cognitive impairment may be related to the sudden reduction of related neuroinflammatory mediators.

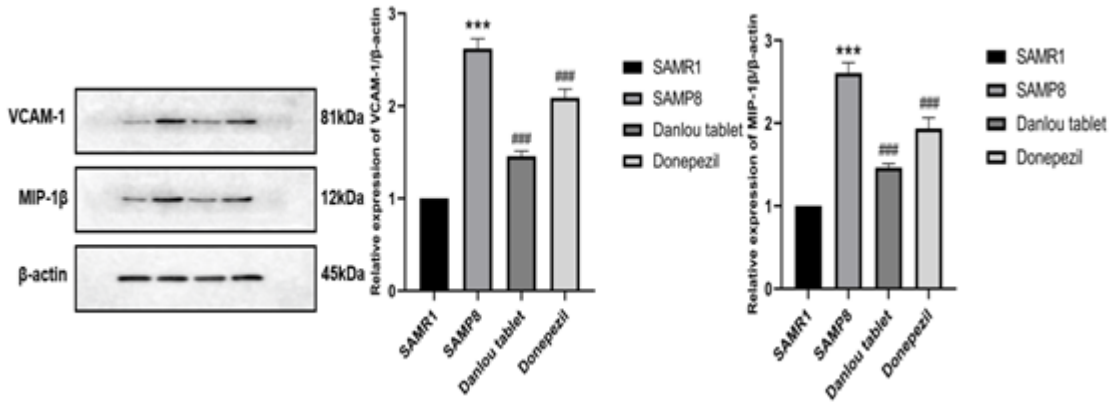

Figure 3: Expression of VCAM-1 and MIP-1β in hippocampus and cortex of mice in each group.

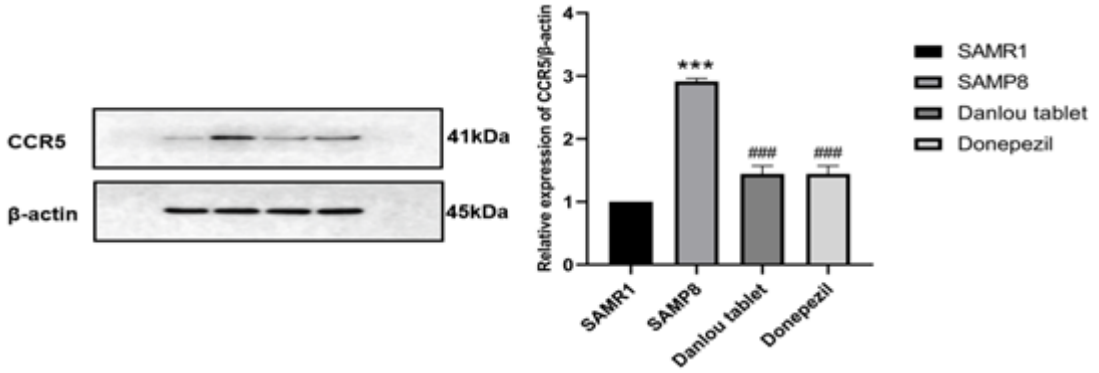

Figure 4: Expression of CCR5 in the hippocampus and cortex of each group.

Activation of ERK1/2 MAPK kinase

Using Western blotting, we detected the phosphorylated form of ERK1/2 in the brains of mice in the SAMR1 control group, SAMP8 group, Danlou tablet treatment group and positive control group. The results showed that compared with the SAMR1 control group, the level of phosphorylated ERK1/2 in the brain extract of the SAMP8 group increased significantly. The phosphorylation of ERK1/2 in the Danlou tablet treatment group was significantly lower than that of the model group **(Figure 5).**

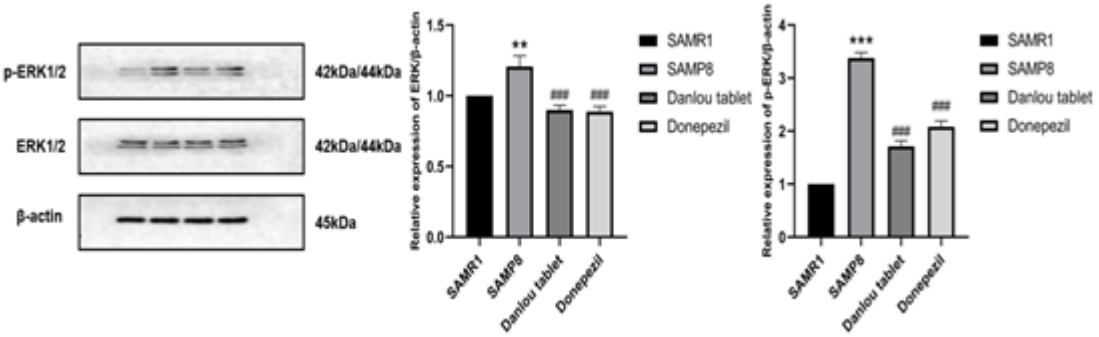

Figure 5: Expression of ERK and p-ERK in hippocampus and cortex of mice in each group.

Discussion

AD is a neurodegenerative disease characterized by memory decline and cognitive impairment. Aβ is produced by hydrolytic cleavage of Amyloid Precursor Protein (APP) under the action of enzymes. APP is produced by α-secretase and undergoes non-amyloid metabolism. α-secretase cleaves APP to generate sAPPα and a C-terminal fragment with 83 amino acids (C83). sAPPα has the functions of neuroprotection and memory enhancement. However, with age, α-secretase will gradually become inefficient. This will cause APP to be truncated by non-

specific proteases (such as β-secretase and γ-secretase), thereby promoting the amyloid cleavage pathway of APP **[11].** APP undergoing the amyloid pathway can produce cytotoxic Aβ, which is an important factor leading to neurotoxicity in AD. Aβ deposited in the brain of AD patients can damage neurons by causing hyperphosphorylation of Tau protein, destroying the blood-brain barrier, and activating glial cells to induce neuro-inflammatory responses, leading to cognitive dysfunction **[12,13].** Chronic persistent neuroinflammatory response is considered to be one of the main pathological features of AD. There is an increase in the number of activated microglia and astrocytes in the brain of AD patients, and high levels of pro-inflammatory factors and immune cells from the periphery adhesion and migration of the central nervous system **[14].** There is chronic inflammation in the brain of AD patients, and the most important morphological feature of inflammation is inflammatory cell infiltration. In the process of inflammatory cell infiltration, the key points include adhesion and chemotaxis **[15].** The role of cell adhesion is the most obvious feature of this molecule in the interaction between leukocytes and endothelial cells and the subsequent transendothelial migration events **[16].** The cell adhesion molecule VCAM-1 is mainly expressed by endothelial cells and participates in the adhesion of lymphocytes and monocytes to endothelium. Human experimental research results show that in the case of BBB destruction, the increase of adhesion molecules originally derived from endothelial cells may infiltrate the central nervous system **[17].** Compared with the normal elderly, the plasma VCAM-1 levels of 60 patients with AD and 80 patients with vascular dementia were increased in the presence of small or large vascular diseases **[18].** In elderly mice, VCAM-1 transmits signals to the brain parenchyma through BMEC, activates microglia, inhibits the activity of neuron precursor cells, and impairs cognitive function. The use of a VCAM-1 antibody can increase the activity of neuron precursor cells, reduce microglia reactivity and hippocampus-dependent improvement in learning and memory **[19].** This finding is consistent with our observations, that is, compared with the control group, the expression level of VCAM-1 in mice in the model group has increased **(Figure 3).** In addition, the chemokine MIP-1β and its receptor CCR5 are important cytokines involved in AD immune regulation. They regulate the transport of immune cells by assisting leukocytes to pass through the brain endothelial cell barrier and their activation, adhesion and transport, activate microglia and astrocytes, induce inflammatory cascades, induce cell migration, and aggravate the progression of AD **[20,21].** To solve this, we first detected the level of MIP-1β in the brain of each group of mice, and found that the level of MIP-1β in the brain of the SAMP8 group was significantly increased **(Figure 3).** Then, we evaluated the expression levels of CCR5 **(Figure 4)** and found that the expression of CCR5 in the SAMP8 group mice was highly up-regulated ($P < 0.01$). In summary, these findings indicate that the levels of VCAM-1, MIP-1β and CCR5 proteins in the

SAMP8 group were significantly increased. These data add to the growing literature supporting the importance of inflammatory mediators in the pathogenesis of AD.

Danlou Tablet is a national-level new Chinese medicine developed by Lei Zhongyi, a master of Chinese medicine, based on the Gualouxiebaijiu Decoction in the Synopsis of the Golden Chamber. It has the effects of invigorating blood and removing blood stasis, resolving phlegm and dispelling congestion. The pharmacological studies of the extract of Danlou tablet have shown that: 1. The alcohol extract of Danlou tablets has the effect of inhibiting the inflammatory response of atherosclerotic endothelial cells **[22]** 2. Its monomer components include gallic acid, salvianolic acid B, Tanshinone IIA, paeoniflorin, daidzein, tanshinone, cryptotanshinone, etc., among which paeoniflorin and tanshinone IIA have a certain effect in improving the cognitive ability of AD mice, reducing neuroinflammatory response and anti-oxidative stress **[23,24].** Salvianolic acid B can improve behavioral defects caused by Lipopolysaccharide (LPS) treatment by inhibiting autophagy and neuroinflammatory response **[25].** In vitro studies have shown that the serum containing Danlou tablet extracts can increase the cell activity after $A\beta_{1-40}$-induced brain microvascular endothelial cell injury and reduce the release of cellular lactate dehydrogenase. Next, we tried to determine through in vivo experiments whether Danlou Tablets can improve cognitive function by reducing Aβ deposition and neuroinflammation in AD. Our findings on mice in the Danlou tablet treatment group highlight the role of Danlou tablets as an inflammation inhibitor in the brains of AD model mice. The effect of Danlou tablet extract is related to the activation of ERK1/2MAPK kinase **(Figure 5).**

Conclusion

In this study, we showed that Danlou tablet extract can reduce the deposition of Aβ in the brain of AD SAMP8 mice. In addition, Danlou tablet extracts reduced the level of MIP-1β in the brain of SAMP8 mice, and down-regulated the expression of VCAM-1 and CCR5, and reduced the inflammation in the brain of AD mice. In the future, Danlou tablet treatment may have significant therapeutic potential and may represent an alternative therapy for the treatment of AD pathological processes.

Declarations

Acknowledgments

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Conflicts of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work is done by the author mentioned in this article, and all the responsibilities involved in the claims related to the content of this article will be borne by the author. Aishe Gao and Zhenqiang Zhang designed the study and supervised the data collection. Sa Yang was responsible for analyzing the data and writing the first draft, and Zijuan Zhang, Junying Song and Hölscher Christian were responsible for reviewing the draft. All authors have read and approved the final manuscript.

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