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Ergothioneine Ameliorates Cognitive Dysfunction in Vascular Dementia Rats by Activating the Nrf2/HO-1 Signaling Pathway: A Postprint

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Abstract

Background Ergothioneine is associated with the severity of cognitive dysfunction in Alzheimer's disease patients and possesses neuroprotective effects. However, whether it can ameliorate cognitive dysfunction in vascular dementia (VD) rats remains unclear, and its specific mechanism of action is not yet understood. Objective To investigate the mechanism by which ergothioneine ameliorates cognitive dysfunction in VD rats through activation of the nuclear factor erythroid 2-related factor 2/heme oxygenase-1 (NRF2/HO-1) signaling pathway. Methods From August 2021 to September 2023, 48 adult male SD rats were selected and randomly divided into control group, model group, ergothioneine group, and ergothioneine+NRF2 inhibitor (ML385) group, with 12 rats in each group. Except for the control group, VD rat models were established in other groups using bilateral common carotid artery permanent ligation. The ergothioneine group received daily intraperitoneal injection of ergothioneine 2 mg/kg starting 2 weeks before modeling for 4 weeks; the ergothioneine+ML385 group received daily intraperitoneal injection of ergothioneine 2 mg/kg and ML385 30 mg/kg starting 2 weeks before modeling for 4 weeks. The effects of ergothioneine on cognitive dysfunction in VD rats were detected through Morris water maze test, HE staining, and TUNEL staining; protein expression levels were detected by Western blotting, and oxidative stress factors and inflammatory factor levels were detected by ELISA. Results The VD rat model was successfully established. Compared with the control group, the model group showed prolonged escape latency, decreased percentage of time spent in the target quadrant ($P<0.05$), reduced number of neurons in hippocampal tissue, cell atrophy, abnormal morphology, deeply stained nuclei, increased neuronal apoptosis rate in brain tissue ($P<0.05$), decreased protein expression levels of NRF2, HO-1, and quinone oxidoreductase 1 (NQO1) in hippocampal tissue ($P<0.05$), decreased levels of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px),

increased malondialdehyde (MDA) level (P<0.05), and increased levels of interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α (P<0.05); compared with the model group, the ergothioneine group showed shortened escape latency, increased percentage of time spent in the target quadrant (P<0.05), alleviated pathological degree of hippocampal tissue, decreased neuronal apoptosis rate in brain tissue (P<0.05), increased protein expression levels of NRF2, HO-1, and NQO1 in hippocampal tissue (P<0.05), increased SOD and GSH-Px levels, decreased MDA level (P<0.05), and decreased levels of IL-1β, TNF-α, and IL-6 (P<0.05); compared with the ergothioneine group, the ergothioneine+ML385 group showed prolonged escape latency, decreased percentage of time spent in the target quadrant (P<0.05), severe hippocampal tissue damage, increased neuronal apoptosis rate in brain tissue (P<0.05), decreased protein expression levels of NRF2, HO-1, and NQO1 in hippocampal tissue (P<0.05), decreased SOD and GSH-Px levels, increased MDA level (P<0.05), and increased levels of IL-1β, TNF-α, and IL-6 (P<0.05). Conclusion Ergothioneine ameliorates cognitive dysfunction in VD rats by activating the NRF2/HO-1 signaling pathway.

Full Text

Ergothioneine Improves Cognitive Dysfunction in Vascular Dementia Rats by Activating the NRF2/HO-1 Signaling Pathway

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Abstract

Background: Ergothioneine is associated with the severity of cognitive impairment in Alzheimer's disease patients and exhibits neuroprotective effects. However, whether it can improve cognitive dysfunction in rats with vascular dementia (VD) remains unclear, and its specific mechanism of action is not yet understood.

Objective: To investigate the mechanism by which ergothioneine improves cognitive dysfunction in VD rats by activating the nuclear factor E2-related factor 2/heme oxygenase-1 (NRF2/HO-1) signaling pathway.

Methods: From August 2021 to September 2023, 48 adult male SD rats were randomly divided into four groups (n=12 each): control, model, ergothioneine,

and ergothioneine + NRF2 inhibitor (ML385). Except for the control group, all groups underwent permanent bilateral common carotid artery ligation to establish a VD rat model. The ergothioneine group received daily intraperitoneal injections of ergothioneine (2 mg/kg) for 4 weeks, starting 2 weeks before modeling. The ergothioneine + ML385 group received daily intraperitoneal injections of ergothioneine (2 mg/kg) and ML385 (30 mg/kg) for 4 weeks, also beginning 2 weeks before modeling. The effects of ergothioneine on cognitive dysfunction in VD rats were assessed using the Morris water maze test, HE staining, and TUNEL staining. Protein expression levels were measured by Western blotting, while oxidative stress and inflammatory factor levels were determined by ELISA.

Results: The VD rat model was successfully established. Compared with the control group, the model group exhibited prolonged escape latency and reduced percentage of time spent in the target quadrant ($P<0.05$), decreased neuronal numbers in the hippocampus with cellular atrophy, morphological abnormalities, and deeply stained nuclei, along with increased neuronal apoptosis rate in brain tissue ($P<0.05$). The model group also showed reduced protein expression of NRF2, HO-1, and quinone oxidoreductase 1 (NQO1) in hippocampal tissue ($P<0.05$), decreased superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) levels, increased malondialdehyde (MDA) level ($P<0.05$), and elevated interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α levels ($P<0.05$). Compared with the model group, the ergothioneine group demonstrated shortened escape latency and increased percentage of time in the target quadrant ($P<0.05$), alleviated hippocampal pathological changes, reduced neuronal apoptosis rate ($P<0.05$), increased expression of NRF2, HO-1, and NQO1 proteins ($P<0.05$), elevated SOD and GSH-Px levels, decreased MDA level ($P<0.05$), and reduced IL-1β, TNF-α, and IL-6 levels ($P<0.05$). Compared with the ergothioneine group, the ergothioneine + ML385 group showed prolonged escape latency, decreased percentage of time in the target quadrant ($P<0.05$), more severe hippocampal damage, increased neuronal apoptosis rate ($P<0.05$), reduced NRF2, HO-1, and NQO1 protein expression ($P<0.05$), decreased SOD and GSH-Px levels, increased MDA level ($P<0.05$), and elevated IL-1β, TNF-α, and IL-6 levels ($P<0.05$).

Conclusion: Ergothioneine improves cognitive dysfunction in VD rats by activating the NRF2/HO-1 signaling pathway.

Keywords: Vascular dementia; NRF2/HO-1 signaling pathway; Oxidative stress reaction; Inflammatory injury; Ergothioneine

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Introduction

Vascular dementia (VD) is one of the most common forms of senile dementia, characterized by high morbidity and mortality rates and decreased quality of life, representing the second leading cause of dementia. As the world enters an aging era, the number of patients with dementia or related cognitive impairments is

projected to increase to 115 million by 2050. Epidemiological surveys indicate that VD accounts for 30% of all dementia patients in Asia. Early prevention and treatment can effectively control disease progression and improve cognitive impairment in patients.

Cerebral ischemic injury is considered the primary pathogenic factor of VD, though its pathogenesis remains incompletely elucidated. Current evidence suggests that VD may be mediated by multiple mechanisms, including oxidative stress, abnormal levels of inflammatory cytokines and chemokines, and mitochondrial dysfunction. Bilateral carotid artery stenosis is accompanied by gradual reduction of cerebral blood flow, and once vascular insufficiency occurs, it promotes the generation of large amounts of reactive oxygen species (ROS) and inflammatory factors, leading to local inflammatory environment formation, antioxidant system suppression, mitochondrial dysfunction, and cellular damage, ultimately causing brain tissue injury and cognitive impairment. Therefore, targeting oxidative stress and inflammatory responses represents a promising therapeutic strategy for VD.

The NRF2/HO-1 signaling pathway plays a crucial role in regulating the expression of various antioxidant defense and anti-inflammatory genes. Studies have demonstrated that the NRF2/HO-1 pathway exerts neuroprotective effects in animal models of VD. Ergothioneine is a naturally occurring betaine amino acid with thiol and thione tautomeric forms. Numerous in vitro studies have shown that ergothioneine can scavenge intracellular ROS, remove reactive nitrogen species such as hydroxyl radicals and peroxynitrite, regulate inflammatory cytokines, and chelate divalent metal cations (such as iron and copper). Additionally, ergothioneine can prevent UV radiation-induced cellular damage and protect cell viability. In neurological diseases, ergothioneine also demonstrates protective effects. In Alzheimer's disease patients, blood ergothioneine concentrations are significantly reduced and correlate with the severity of cognitive impairment. However, whether ergothioneine improves cognitive dysfunction in VD rats by modulating the NRF2/HO-1 signaling pathway remains poorly understood. This study established a VD rat model to investigate the effects of ergothioneine on cognitive dysfunction and its specific molecular mechanisms.

Materials and Methods

Study Period: August 2021 to September 2023.

Experimental Animals: Fifty SPF-grade adult male SD rats, weighing 200-230 g, were obtained from Hunan Slack Jingda Laboratory Animal Co., Ltd. (License No. SCXK (Xiang) 2016-0002). The animals were housed in a controlled environment with temperature $(22\$\pm2)°C, humidity(55\pm\$10)\%$, and a 12-hour light/dark cycle with free access to food and water. This study was approved by the Medical Ethics Committee of the First Hospital of Changsha [Ethics Approval No.: (2023) Ethics Review [Clinical Research] No. (66)].

Experimental Reagents: Ergothioneine (Sigma-Aldrich, USA, Cat. No. E7521); NRF2 inhibitor (ML385) (MedChemExpress, USA, Cat. No. HY-100523); sodium pentobarbital (Beijing Coupling Technology Co., Ltd., Cat. No. OH004809); sodium nitroprusside (Sigma-Aldrich, USA, Cat. No. PHR1423); superoxide dismutase (SOD) assay kit, interleukin (IL)-1β assay kit, IL-6 assay kit, and tumor necrosis factor (TNF)-α assay kit (all from R&D Systems, USA, Cat. No. DYC3419, MLB00C, MLB00C, MTA00B); malondialdehyde (MDA) assay kit (Abcam, USA, Cat. No. ab238537); glutathione peroxidase (GSH-Px) assay kit (Shanghai Enzyme-linked Biotechnology, Cat. No. ml097316); NRF2 rabbit monoclonal antibody, HO-1 mouse monoclonal antibody, and quinone oxidoreductase 1 (NQO1) goat polyclonal antibody (all from Abcam, USA, Cat. No. ab62352, ab13248, ab2346).

Experimental Instruments: Morris water maze (Shanghai Yuyan Scientific Instruments Co., Ltd., Model YAN-MWMR); optical microscope (OLYMPUS, Japan, Model CKX53); fluorescence microscope (OLYMPUS, Japan, Model CX31); enzyme-linked immunosorbent assay detector (Nanjing Huadong, Model DG5033A).

Animal Model Establishment: The VD rat model was established by permanent bilateral common carotid artery ligation. The model and drug treatment groups underwent bilateral common carotid artery ligation, while the control group only had bilateral common carotid arteries and nerves separated without ligation. Briefly, rats were anesthetized by intraperitoneal injection of 3% sodium pentobarbital (45 mg/kg), fixed in supine position, and underwent routine disinfection. A midline neck incision was made to isolate the bilateral common carotid arteries. The model group received intraperitoneal injection of sodium nitroprusside solution (2.5 mg/kg), followed by bilateral common carotid artery occlusion for 10 minutes and reperfusion for 10 minutes, repeated twice before wound closure. Rats were returned to their cages for recovery. One week post-surgery, all groups underwent Morris water maze training for one day. Using the mean escape latency of the control group as reference, rats with a difference between their post-surgery mean escape latency and the reference value accounting for >20% of the control group's mean escape latency were defined as demented.

Drug Treatment: The ergothioneine group received daily intraperitoneal injections of ergothioneine (2 mg/kg) for 2 weeks before modeling and continued for 2 weeks after modeling. The ergothioneine + ML385 group received daily intraperitoneal injections of ergothioneine (2 mg/kg) and ML385 (30 mg/kg) for 2 weeks before modeling and continued for 2 weeks after modeling.

Morris Water Maze Test: The test consisted of two parts. (1) **Place Navigation Trial:** Rats were trained 4 times daily for 4 consecutive days, with intervals >30 minutes between each trial. For each trial, one of four pool wall starting points was randomly selected (each starting point used only once per day). Rats were placed in the water, and the system recorded the time to find the platform as escape latency. If a rat failed to find the platform within 120

seconds, it was recorded as 120 seconds, and the rat was allowed to rest on the platform for 30 seconds before the next trial. (2) **Spatial Probe Test:** On day 5, a single platform-free trial was conducted with the rat starting from quadrant I. The 120-second trial recorded time spent in quadrant III, calculating the percentage of time in the target quadrant. The first test was performed before drug administration to screen eligible rats, and retesting after 4 weeks of intraperitoneal drug administration evaluated inter-group differences.

HE Staining: Paraffin-embedded sections were dewaxed with xylene and dehydrated with graded ethanol. Sections were stained with hematoxylin solution, differentiated in acid and ammonia water, rinsed under running water, and placed in distilled water. After dehydration in 70% and 90% ethanol, sections were stained with alcoholic eosin solution for 2-3 minutes, dehydrated with pure ethanol, cleared with xylene, sealed with neutral resin, and observed under an optical microscope.

TUNEL Staining: After proteinase K tissue repair, 50 L of TUNEL staining solution was added to each sample and incubated at 37°C for 60 minutes. Following three PBS washes, sections were mounted with DAPI anti-fluorescence quenching solution and examined under a fluorescence microscope.

Western Blotting: Samples were collected, minced, and homogenized in ice bath. RIPA lysis buffer (containing protease inhibitors) was added to facilitate protein release and prevent degradation. Total tissue protein was extracted, and protein concentration was determined by BCA method. Protein expression levels of NRF2, HO-1, and NQO1 in hippocampal tissue were detected through electrophoresis, membrane transfer, blocking, antibody incubation, and film development.

ELISA Assay: Hippocampal tissue was removed, washed with 0.9% sodium chloride solution, and placed in a homogenization tube. Appropriate amount of 0.9% sodium chloride solution (4°C) was added to homogenize the tissue, and the supernatant was collected. Specific ELISA kits were used according to the manufacturer's instructions to detect oxidative stress markers (SOD, MDA, GSH-Px) and inflammatory factors (IL-1β, IL-6, TNF-α) in hippocampal tissue.

Statistical Analysis: Data were analyzed using SPSS 22.0 statistical software. Normally distributed measurement data were expressed as (x-$\pm$s). Inter-group comparisons were performed using one-way ANOVA, with pairwise comparisons conducted using LSD-t test. $P<0.05$ was considered statistically significant.

Results

Effects of Ergothioneine on Cognitive Dysfunction in VD Rats

The VD rat model was successfully established. Compared with the control group, the model group showed prolonged escape latency and reduced percent-

age of time spent in the target quadrant (P<0.05). Ergothioneine treatment shortened the escape latency and increased the percentage of time in the target quadrant compared with the model group (P<0.05). The ergothioneine + ML385 group exhibited prolonged escape latency and decreased percentage of time in the target quadrant compared with the ergothioneine group (P<0.05) .

Effects of Ergothioneine on Hippocampal Pathological Changes in VD Rats

HE staining results demonstrated that compared with the control group, the model group exhibited reduced neuronal numbers in the hippocampus, cellular atrophy, morphological abnormalities, and deeply stained nuclei. These abnormalities were alleviated by ergothioneine treatment. In contrast, the ergothioneine + ML385 group showed more severe hippocampal damage compared with the ergothioneine group [Figure 1: see original paper].

Effects of Ergothioneine on Neuronal Apoptosis in VD Rat Brain Tissue

Compared with the control group, the model group showed increased neuronal apoptosis rate in brain tissue (P<0.05). Ergothioneine treatment reduced the neuronal apoptosis rate compared with the model group (P<0.05). The ergothioneine + ML385 group exhibited increased apoptosis rate and more severe hippocampal damage compared with the ergothioneine group (P<0.05) [Figure 2: see original paper].

Effects of Ergothioneine on NRF2, HO-1, and NQO1 Protein Expression in VD Rat Hippocampus

Compared with the control group, the model group showed decreased protein expression levels of NRF2, HO-1, and NQO1 in hippocampal tissue (P<0.05). Ergothioneine treatment increased the expression of these proteins compared with the model group (P<0.05). The ergothioneine + ML385 group exhibited reduced expression of NRF2, HO-1, and NQO1 proteins compared with the ergothioneine group (P<0.05) [Figure 3: see original paper].

Effects of Ergothioneine on Oxidative Stress Factors SOD, GSH-Px, and MDA in VD Rat Hippocampus

The model group showed decreased SOD and GSH-Px levels and increased MDA level compared with the control group (P<0.05). Ergothioneine treatment increased SOD and GSH-Px levels while decreasing MDA level compared with the model group (P<0.05). The ergothioneine + ML385 group exhibited decreased SOD and GSH-Px levels and increased MDA level compared with the ergothioneine group (P<0.05) .

Effects of Ergothioneine on Inflammatory Factors IL-1β, TNF-α, and IL-6 in VD Rat Hippocampus

Compared with the control group, the model group showed increased levels of IL-1β, TNF-α, and IL-6 in hippocampal tissue (P<0.05). Ergothioneine

treatment reduced these inflammatory factor levels compared with the model group ($P<0.05$). The ergothioneine + ML385 group exhibited increased IL-1β, TNF-α, and IL-6 levels compared with the ergothioneine group ($P<0.05$) .

Discussion

VD pathogenesis involves multiple mechanisms including inflammation, oxidative stress, amyloid angiopathy, and metabolic disorders. Elevated inflammatory markers may underlie neurovascular unit injury, as inflammation and oxidative stress damage can alter neuronal and white matter function by interfering with neurovascular coupling. In this study, during the first water maze test after VD modeling, 36 out of 38 rats showed a difference between their mean escape latency and the reference value accounting for >20% of the control group's mean escape latency, indicating successful modeling. In the water maze test after drug administration, the model and treatment groups showed prolonged escape latency compared with the control group, indicating impaired learning ability regarding spatial markers. The reduced percentage of time spent in the target quadrant indicated impaired memory for spatial markers, suggesting learning and memory deficits in VD model rats. Furthermore, this study demonstrated that ergothioneine improved spatial learning and memory abilities and alleviated hippocampal pathological changes in VD rats. After ergothioneine administration, VD rats showed reduced hippocampal apoptosis rate and suppressed oxidative stress and inflammatory damage, while ML385 reversed these beneficial effects of ergothioneine.

This study indicates that ergothioneine can improve cognitive impairment in VD rats by activating the NRF2/HO-1 signaling pathway. Ergothioneine is a natural potent antioxidant that can directly neutralize ROS and xenobiotics, regulate protein structure and function, and act as a cofactor for antioxidant and metabolic enzymes, exerting antioxidant and anti-inflammatory effects. Studies have also demonstrated its neuroprotective, cardiovascular protective, and hepatoprotective properties. Due to its strong antioxidant capacity, high stability, non-toxicity, and ability to cross the blood-brain barrier, ergothioneine shows promising therapeutic potential for central nervous system diseases.

The NRF2/HO-1 signaling pathway is a key cellular antioxidant defense pathway. NRF2 can regulate the expression of multiple antioxidants and phase II detoxifying enzymes (HO-1, NQO1, SOD) through antioxidant response elements (ARE). HO-1 catalyzes the degradation of pro-oxidant heme to produce carbon monoxide, iron, and biliverdin, thereby exerting anti-inflammatory, antioxidant, and anti-apoptotic effects. Numerous studies have shown that upregulating HO-1 expression helps cells resist external stimuli and inhibits oxidative stress damage. The NRF2/HO-1 pathway also demonstrates neuroprotective effects in other cognitive impairment diseases such as Alzheimer's disease.

Research has shown that ergothioneine exerts antioxidant functions by acti-

vating the NRF2/HO-1 pathway. Ergothioneine can prevent UVB irradiation-induced alterations in collagen homeostasis in dermal fibroblasts, protect keratinocytes by inhibiting ROS production and cleavage of pro-apoptotic proteins (including Caspase-8 and PARP), and reduce paracrine cytokines including IL-1β, IL-6, and TNF-α. Ergothioneine can also prevent diabetes-induced cardiovascular injury by upregulating the Keap1-NRF2 pathway and its downstream cytoprotective antioxidants. In this study, after establishing the VD rat model by permanent bilateral common carotid artery ligation, protein expression levels of NRF2, HO-1, and NQO1 in the hippocampus were reduced. Ergothioneine increased the expression of these proteins in VD rat hippocampus, protecting against oxidative stress damage and inflammatory responses and improving cognitive dysfunction.

In summary, ergothioneine can inhibit apoptosis, oxidative stress damage, and inflammation in the hippocampus of VD rats by activating the NRF2/HO-1 signaling pathway. However, this study did not investigate the mechanism of ergothioneine in VD in vitro models, nor was it validated in clinical trials, representing certain limitations. Therefore, future research will further explore the effects of ergothioneine on VD at both clinical and cellular levels.

Author Contributions

LIU Qingfang was responsible for experimental design and conceptualization and takes responsibility for the article. CAO Tianran organized the project implementation, controlled experimental quality, and was responsible for drafting, revising, and reviewing the manuscript. WEI Youshi, XIAO Fei, and ZHOU Chunxiang conducted animal experiments and related index detection. LIU Qun and YUAN Hui were responsible for data collation and statistical analysis.

This article has no conflicts of interest.

References

[1] FREDERIKSEN K S, COOPER C, FRISONI G B, et al. A European Academy of Neurology guideline on medical management issues in dementia[J]. Eur J Neurol, 2020, 27(10): 1805-1820. DOI: 10.1111/ene.14412.

[2] BAI W, CHEN P, CAI H, et al. Worldwide prevalence of mild cognitive impairment among community dwellers aged 50 years and older: a meta-analysis and systematic review of epidemiology studies[J]. Age Ageing, 2022, 51(8): afac173. DOI: 10.1093/ageing/afac173.

[3] WOLTERS F J, IKRAM M A. Epidemiology of vascular dementia pathogenesis and treatment[J]. Arterioscler Thromb Vasc Biol, 2019, 39(8): 1542-1549. DOI: 10.1161/ATVBAHA.119.311908.

[4] ZHU M L, ZHANG J, GUO L J, et al. Amorphous selenium inhibits oxidative stress injury of neurons in vascular dementia rats by activating NMDAR pathway[J]. Eur J Pharmacol, 2023, 955: 175874. DOI: 10.1016/j.ejphar.2023.175874.

[5] LIAO X P, ZHANG Z L, MING M, et al. Imperatorin exerts antioxidant effects in vascular dementia via the Nrf2 signaling pathway[J]. Sci Rep, 2023, 13(1): 5595. DOI: 10.1038/s41598-022-21298-x.

[6] WU S, HUANG R, ZHANG R Q, et al. Gastrodin and gastrodigenin improve energy metabolism disorders and mitochondrial dysfunction to antagonize vascular dementia[J]. Molecules, 2023, 28(6): 2598. DOI: 10.3390/molecules28062598.

[7] ZHU J Y, DU J, KOU W H, et al. Probucol protects against brain damage caused by intra-neural pyroptosis in rats with vascular dementia through inhibition of the Syk/Ros pathway[J]. Aging, 2024, 16(5): 4363-4377. DOI: 10.18632/aging.205593.

[8] BRUNETTI D, CATANIA A, VISCOMI C, et al. Role of PITRM1 in mitochondrial dysfunction and neurodegeneration[J]. Biomedicines, 2020, 8(8): 283. DOI: 10.3390/biomedicines8080283.

[9] KOPACZ A, KLOSKA D, FORMAN H J, et al. Beyond repression of Nrf2: an update on Keap1[J]. Free Radic Biol Med, 2020, 157: 63-74. DOI: 10.1016/j.freeradbiomed.2020.03.023.

[10] PANG Q Q, ZANG C X, LI T, et al. Neuroprotective effect of GJ-4 against cognitive impairments in vascular dementia by improving white matter damage[J]. Phytomedicine, 2024, 132: 155877. DOI: 10.1016/j.phymed.2024.155877.

[11] CORDARO M, D'AMICO R, FUSCO R, et al. Discovering the effects of fisetin on NF- B/NLRP-3/NRF-2 molecular pathways in a mouse model of vascular dementia induced by repeated bilateral carotid occlusion[J]. Biomedicines, 2022, 10(6): 1448. DOI: 10.3390/biomedicines10061448.

[12] BORODINA I, KENNY L C, MCCARTHY C M, et al. The biology of ergothioneine, an antioxidant nutraceutical[J]. Nutr Res Rev, 2020, 33(2): 190-217. DOI: 10.1017/S0954422419000301.

[13] WHITMORE C A, HAYNES J R, BEHOF W J, et al. Longitudinal consumption of ergothioneine reduces oxidative stress and amyloid plaques and restores glucose metabolism in the 5XFAD mouse model of Alzheimer's disease[J]. Pharmaceuticals, 2022, 15(6): 742. DOI: 10.3390/ph15060742.

[14] BEHOF W J, WHITMORE C A, HAYNES J R, et al. Improved synthesis of an ergothioneine PET radioligand for imaging oxidative stress in Alzheimer's disease[J]. FEBS Lett, 2022, 596(10): 1279-1289. DOI: 10.1002/1873-3468.14303.

[15] WU L Y, CHEAH I K, CHONG J R, et al. Low plasma ergothioneine levels are associated with neurodegeneration and cerebrovascular

disease in dementia[J]. Free Radic Biol Med, 2021, 177: 201-211. DOI: 10.1016/j.freeradbiomed.2021.10.019.

[16] NGUYEN D H, CUNNINGHAM J T, SUMIEN N. Estrogen receptor involvement in vascular cognitive impairment and vascular dementia[J]. Geroscience, 2021, 43(1): 159-166. DOI: 10.1007/s11357-020-00263-4.

[17] CUSTODERO C, CIAVARELLA A, PANZA F, et al. Role of inflammatory markers in the diagnosis of vascular contributions to cognitive impairment and dementia: a systematic review and meta-analysis[J]. Geroscience, 2022, 44(3): 1373-1392. DOI: 10.1007/s11357-022-00556-w.

[18] ULRICH K, JAKOB U. The role of thiols in antioxidant systems[J]. Free Radic Biol Med, 2019, 140: 14-27. DOI: 10.1016/j.freeradbiomed.2019.05.035.

[19] KOH S S, OOI S C, LUI N M, et al. Effect of ergothioneine on 7-ketocholesterol-induced endothelial injury[J]. Neuromolecular Med, 2021, 23(1): 184-198. DOI: 10.1007/s12017-020-08616-8.

[20] BEHOF W J, WHITMORE C A, HAYNES J R, et al. A novel antioxidant ergothioneine PET radioligand for in vivo imaging applications[J]. Sci Rep, 2021, 11(1): 18450. DOI: 10.1038/s41598-021-97925-w.

[21] SMITH EINAR, OTTOSSON FILIP, HELLSTRAND SOPHIE, et al. Ergothioneine may reduce the risk and mortality of cardiovascular disease[J]. Chin J Br Med, 2020, 23(4): 1. DOI: 10.3760/cma.j.issn.1007-9742.2020.04.115.

[22] LORETO R G, HUGHES D P. The metabolic alteration and apparent preservation of the zombie ant brain[J]. J Insect Physiol, 2019, 118: 103918. DOI: 10.1016/j.jinsphys.2019.103918.

[23] TERUYA T, CHEN Y J, KONDOH H, et al. Whole-blood metabolomics of dementia patients reveal classes of disease-linked metabolites[J]. Proc Natl Acad Sci USA, 2021, 118(37): e2022857118. DOI: 10.1073/pnas.2022857118.

[24] LI Fuzhang. Regular mushroom consumption can reduce the probability of cognitive impairment[J]. Family Medicine (First Half), 2019(9): 1.

[25] ZHANG Ruihu, YAO Ru, SHI Zeya, et al. Liensinine exerts anti-inflammatory and antioxidant effects by inhibiting NF- B and activating the Nrf2/HO-1 pathway[J]. Chin J Exp Anim, 2022, 30(2): 191-197. DOI: 10.3969/j.issn.1005-4847.2022.02.006.

[26] SUN Y Y, ZHU H J, ZHAO R Y, et al. Remote ischemic conditioning attenuates oxidative stress and inflammation via the Nrf2/HO-1 pathway in MCAO mice[J]. Redox Biol, 2023, 66: 102852. DOI: 10.1016/j.redox.2023.102852.

[27] LIU Feng, LIU Zengzhang. Pachymic acid ameliorates OX-LDL-induced human umbilical vein endothelial cell injury by activating the Nrf2/HO-1 signaling pathway[J]. Chin J Immunol, 2020, 36(2): 164-168, 179. DOI: 10.3969/j.issn.1000-484X.2020.02.007.

[28] YAN R, YAN J F, CHEN X Z, et al. Xanthoangelol prevents ox-LDL-induced endothelial cell injury by activating Nrf2/ARE signaling[J]. J Cardiovasc Pharmacol, 2019, 74(2): 162-171. DOI: 10.1097/FJC.0000000000000699.

[29] ZHANG Y, CHEN J T, WU H D, et al. Hydrogen regulates mitochondrial quality to protect glial cells and alleviates sepsis-associated encephalopathy by Nrf2/YY1 complex promoting HO-1 expression[J]. Int Immunopharmacol, 2023, 118: 110009. DOI: 10.1016/j.intimp.2023.110009.

[30] CHEN Z M, ZHONG H, WEI J S, et al. Inhibition of Nrf2/HO-1 signaling leads to increased activation of the NLRP3 inflammasome in osteoarthritis[J]. Arthritis Res Ther, 2019, 21(1): 300. DOI: 10.1186/s13075-019-2085-6.

[31] LI L, LI W J, ZHENG X R, et al. Eriodictyol ameliorates cognitive dysfunction in APP/PS1 mice by inhibiting ferroptosis via vitamin D receptor-mediated Nrf2 activation[J]. Mol Med, 2022, 28(1): 11. DOI: 10.1186/s10020-022-00442-3.

[32] WEI C, FAN J, SUN X, et al. Acetyl-11-keto-β-boswellic acid ameliorates cognitive deficits and reduces amyloid-β levels in APPswe/PS1dE9 mice through antioxidant and anti-inflammatory pathways[J]. Free Radic Biol Med, 2020, 150: 96-108. DOI: 10.1016/j.freeradbiomed.2020.02.022.

[33] KO H J, KIM J, AHN M, et al. Ergothioneine alleviates senescence of fibroblasts induced by UVB damage of keratinocytes via activation of the Nrf2/HO-1 pathway and HSP70 in keratinocytes[J]. Exp Cell Res, 2021, 400(1): 112516. DOI: 10.1016/j.yexcr.2021.112516.

[34] DARE A, ELRASHEDY A A, CHANNA M L, et al. Cardioprotective effects and in-silico antioxidant mechanism of L-ergothioneine in experimental type-2 diabetic rats[J]. Cardiovasc Hematol Agents Med Chem, 2022, 20(2): 133-147. DOI: 10.2174/1871525719666210809122541.

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Note: Figure translations are in progress. See original paper for figures.

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