Effect of Noni on memory impairment induced by hydrocortisone in mice

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Abstract

Background

Oxidative stress and memory impairment have been implicated, a common functional brain disease. Nuclear factor E2-related factor 2 (Nrf2) is highly induced in oxidative stress, indicating that Nrf2 is an emerging target of memory therapy. This study aimed to investigate the effect of Noni on brain memory impairment induced by hydrocortisone and its protection mechanism in mice.

Methods

Male Kuming mice were (n = 8/group) given hydrocortisone by gastric gavage for 14 consecutive days to establish the memory impairment model except for those in the control group. At the same day, the corresponding drugs were given by gastric gavage. The changes in ethology were examined. Brains were extracted and subjected to western blot analysis and biochemical analyses to assess the activities of oxidative stress.

Results

The middle and high-dose Noni groups ameliorated the ethology and the high-dose Noni group increased cerebral protein expressions of Nrf2, kelch-like ECH-associated protein 1 (KEAP1) and heme oxygenase-1 (HO-1), as compared to the model group. The arrangement of CA3 vertebral cells in hippocampus of mice was slightly compact and hyperchromatic and pyknosis were alleviated. Furthermore, the biochemical analyses showed the activities of related enzymes of oxidative stress in high-dose Noni group were increased.

Conclusions

Noni might be a powerful antioxidant that can protect nerve cell and may possess as a potential benefit for the treatment of memory impairment.

Background

Noni (*Morinda citrifolia* Linn) originally from Polynesia, is widely distributed in the southern Pacific islands and the Indo China Peninsula. It has been used in herbal remedies to treat and prevent various kinds of diseases by indigenous people[1] and it shows strong antioxidant capacity[2, 3]. Noni has been cultivated in Hainan and Yunnan provinces of China since being introduced to China. In 2010, Noni fruit juice was approved as a new resource food by the Ministry of Health of China for the first time. What's more, some related beverages such as Xisha Noni®, Mornida® have been widely used and also have several dietary supplements which contain Chinese traditional functional food like Ginseng or Cornus

officinalis. Researches show Noni can improve memory[4, 5]. Noni has been reported to prevent amyloid beta induced memory impairment in mice[6] and scopolamine induced memory impairment in mice[7]. However, the mechanism is still unclear. It may be caused by pathological or situational reasons.

Noni is reported to have potent antioxidant and neuroprotective effects in animal models[8]. Oxidative stress is a major factor involved in the development and progression of dementia[9]. Memory impairment is closely related to oxidative stress[10]. Excessive oxidative stress can not only cause neuronal cell damage[11], but also lead to brain tissue damage. It has been reported that oxidative stress is related to Nrf2/Keap1/HO-1 pathway[12]. Nuclear factor E2-related factor 2 (Nrf2) is an essential regulator to induce the gene expression of phase II enzyme and heme oxygenase-1 (HO-1) in phase II enzyme has protective effect on cells[13]. In our study, the powerful antioxidant capacity of Noni as the breakthrough point to explore the mechanism of noni which could improve memory and provide experimental basis for further development of memory products.

In this study, we investigated the effect of Noni on memory impairment induced by hydrocortisone in mice to investigate the mechanism of the neuroprotective effect, with particular emphasis on brain oxidative stress.

Methods

Experimental Animals.

Forty-eight healthy male Kunming mice, weighing 20 ± 2g, were provided by SPF (Beijing) biotechnology Company Limited [animal qualification certificate No. SCXK (Jing)-2016-0002] and were allowed to acclimatize for 3 days before the experiment. The mice were housed 4 per cage and maintained under a 12:12h light/dark cycle at 55% humidity and 22 ± 2 ℃ with free access to food and water. Procedures involving mice were approved by the Institutional Animal Care and Use Committee of Beijing University of Chinese Medicine. (BUCM-4-20190102-3008)

Drugs, Reagents and Instruments.

The dry powder of noni fruit juice aqueous extract was provided by Morinda Inc. The Noni powder was dissolved in water and prepared to a concentration of 0.5mg/10mL. Hydrocortisone injection was provided by Tianjin Kingyork Ltd.(lot.1801181). Total superoxide dismutase, Copper/Zinc superoxide dismutase, Manganese superoxide dismutase (T-SOD, CuZn-SOD, Mn-SOD), Catalase (CAT), Lipid peroxidation (LPO) and Malondialdehyde (MDA) kits were obtained from Nanjing Jiancheng Bioengineering Institute (lot.20200724,20200806,20200822,20200729). Anti-Nrf2, anti-KEAP1, anti-HO-1 and anti-β-Actin were all purchased from Bioss (Beijing, China) (lot.BJ07138310, BJ07012178, BJ02265489, AH11286487).

Grouping, Modeling and Experimental Design.

Forty-eight male Kunming mice were divided into 6 groups using a random number table, with 8 in each group: the control group, the model group (double distilled water 10mL/kg), the Ginseng group (1g/kg), the high-dose Noni group (1.33g/kg, H-Noni), the middle-dose Noni group (0.67g/kg, M-Noni), and the low-dose Noni group (0.33g/kg, L-Noni). The 40 rats were given hydrocortisone (15mg/kg) by gastric gavage for 14 consecutive days to establish the memory impairment model[14] except for those in the control group. At the same day, the corresponding drugs were administered were given by gastric gavage. The weight, brain index and behavior of the mice in each group were observed. There were no accidental deaths among the mice during the experiment. After the experiment, mice were killed by cervical dislocation and brain tissues were separated and stored at − 80℃ for analysis.

Measurement of Mouse Body Weight and Brain Index.

Each mouse was weighed weekly. The wet weight of the brain tissue was measured using a balance and the brain index (BI) was calculated as follows: BI = brain wet weight/mouse weight×100%.

Ethology Assessments.

Ethology was assessed with the step-down test and passive avoidance test. Incubation period is the time from the mice which were placed on the insulated platform in the box to the first time they jumped off the platform. Training phase is after 3min of acclimatization in a dark box, the mice were stimulated with immediate 36V alternating current and then placed on the platform for an acclimatization period. The incubation period and the number of errors in jumping off the platform within 5min were recorded. After 5d of cessation of training, the vanish test was performed. The incubation period was the time from the time each mouse was placed in the open chamber to the time when it was first shocked in the dark chamber. Since mice are nocturnal animals and instinctively flee to the dark, the electric shock was used to train their spatial learning and memory. The training phase: each mouse was put into the open chamber, the door was raised after 5s, the door was closed as soon as the animal entered the dark chamber completely, and an unavoidable electric shock of 36V was delivered to the mouse's feet for 2s. Then the mouse was moved to the open chamber and the process was repeated after 5min. The training was terminated when the mice remained in the light room for 5min. 24h later, the incubation period and the number of errors in entering the dark room within 5min were recorded for each mouse. The training was stopped for 5d, and the vanish test was performed.

Brain histology.

All brain tissues were fixed in 4% paraformaldehyde buffer for 36h and embedded in paraffin. Sections were cut at 4.0 μm and stained with hematoxylin and eosin (HE staining) for histopathologic examinations using standard protocols, all of the images were acquired with a Digital Pathology system Axio Scan.Z1 (Zeiss, Germany) for assessment the nerve cell.

Biochemical Assays.

The measurement of activities of T-SOD, CuZn-SOD, Mn-SOD, CAT, LPO and content of MDA tested in strict accordance with the instructions of the kit.

Western Blot Analysis.

After adding protease inhibitor, brain tissues were prepared on ice. The supernatants were centrifuged at 4000g and the tests were carried out strictly according to the instructions of the kit. Total protein was extracted from brain tissues in each group, and protein was quantified according to the bicinchoninic acid protein quantification kit instructions (Nanjing Jiancheng, China). Proteins were separated by 10% SDS-PAGE and transferred by electrophoresis onto polyvinylidene fluoride membranes, then incubated with TBST containing 5% no-fat milk at room temperature for 1 h, and then washed 5 times with TBST for 5 min each. Diluted Nrf2 (1:500), KEAP1(1:1000), HO-1(1:1000) and β-Actin antibodies (1:5000) were added separately, and the membranes were incubated overnight at 4℃. The next day, the membranes were rinsed 5 times with TBST for 5 min each, and the corresponding horseradish peroxidase-labelled secondary antibody (1:5000) was added. The membranes were incubated for 1 h at room temperature and then rinsed 5 times in TBST for 5 min each. The films were rapidly developed according to the electron chemiluminescence kit instructions (New Cell & Molecular Biotech, China). Image J software was utilized for the quantitative analysis of images. Each experiment for each protein was repeated 3 times.

Statistical Analysis.

Analysis was performed using SPSS (version 22.0, SPSS Inc., Chicago, IL, USA). The measurement data are represented as mean ± standard deviation ($\bar{x}$±s). One-way ANOVA analysis followed by the Bonferoni method was adopted to compare the sample mean pairs. Values of $p < 0.05$ were considered statistically significant.

Results

Noni Had no effect on weight and BI in memory impairment mice.

During the experiment, the activity of mice in each group was normal, and the hair color was normal. There was no significant difference in body weight and brain index after modeling and medication ($P > 0.05$). Hydrocortisone, Noni and Ginseng had no effect on body weight and brain weight (Table 1).

Table 1

Weight of mice and BI($\bar{x}$± s,n = 8)

Group	7d weight (g)	14d weight (g)	BI(%)
Control	25.59 ± 0.85	42.36 ± 2.13	0.72 ± 0.08
Model	25.59 ± 0.63	39.47 ± 2.23	0.79 ± 0.09
Ginseng	25.29 ± 0.89	39.03 ± 4.23	0.79 ± 0.08
H-Noni	25.32 ± 0.62	38.49 ± 3.54	0.79 ± 0.04
M-Noni	25.56 ± 1.07	39.04 ± 2.67	0.77 ± 0.07
L-Noni	25.05 ± 0.86	38.14 ± 3.07	0.77 ± 0.06
Noni ameliorated ethology behavior in memory impairment mice.			

Step down avoidance test and passive avoidance test results showed that the time in center, distance in center and overall distance traveled in the control group were shorter than those in the model group (p < 0.01). Ginseng group and High-dose Noni group significantly increased the abovementioned indices (p < 0.01). Compared with the model group, both the time in center and distance in center in the Ginseng group and High-dose Noni group were decreased (both p < 0.05), but there was no significant difference in overall distance traveled between the two groups (Table 2 Table 3).

Table 2

Effects of Noni on step down avoidance test in mice($\bar{x}$± s, n = 8)

Group	Incubation period (s)	Error time	Vanish period (s)	Vanish error time
Control	145.9 ± 2.9	3.0 ± 2.1	181.8 ± 4.7	1.5 ± 0.9
Model	72.1 ± 8.2**	5.9 ± 1.4**	97.6 ± 6.0**	4.1 ± 1.1**
Ginseng	99.3 ± 12.9$^{\#\#}$	2.5 ± 1.3$^{\#\#}$	155.6 ± 8.4$^{\#\#}$	1.6 ± 0.7$^{\#\#}$
H-Noni	120.4 ± 11.0$^{\#\#}$	3.0 ± 0.9$^{\#\#}$	163.4 ± 9.2$^{\#\#}$	1.5 ± 0.9$^{\#\#}$
M-Noni	90.1 ± 11.3$^{\#\#}$	3.1 ± 1.7$^{\#\#}$	135.3 ± 7.4$^{\#\#}$	3.0 ± 0.8$^{\#}$
L-Noni	79.3 ± 6.2	4.6 ± 1.5	104.1 ± 10.6	4.0 ± 0.8
Notes: vs. control group **p < 0.01; vs. model group $^{\#}$p < 0.05, $^{\#\#}$p < 0.01				

Table 3

Effects of Noni on passive avoidance test in mice($\bar{x}$ ± s, n = 8)

Group	Incubation period (s)	Error time	Vanish period (s)	Vanish error time
Control	49.5 ± 6.5	2.0 ± 1.7	132.3 ± 8.3	2.0 ± 1.7
Model	31.5 ± 6.1**	4.1 ± 1.1**	80.3 ± 6.2**	4.0 ± 1.2**
Ginseng	58.1 ± 6.4$^{\#\#}$	1.9 ± 0.8$^{\#\#}$	115.8 ± 10.4$^{\#\#}$	2.1 ± 1.0$^{\#\#}$
H-Noni	46.4 ± 6.7$^{\#\#}$	2.0 ± 1.1$^{\#\#}$	124.9 ± 14.2$^{\#\#}$	2.4 ± 1.2$^{\#\#}$
M-Noni	38.5 ± 5.0$^{\#}$	3.9 ± 0.8	123.0 ± 5.1$^{\#\#}$	3.6 ± 0.7
L-Noni	29.0 ± 4.4	4.4 ± 0.7	108.0 ± 9.0$^{\#\#}$	4.1 ± 1.0
Notes: vs. control group $^{**}p < 0.01$; vs. model group $^{\#\#}p < 0.01$				

Pathology of Brain Tissue of Mice in Each Group.

In control group, the neurons in CA3 area of hippocampus were arranged in a compact and orderly manner. Compared with the control group, the vertebral cells in the CA3 area of hippocampus in the model group were loosely arranged, with obvious deep staining or pyknosis. Compared with the model group, the arrangement of neurons in hippocampal CA3 area of each treatment group was slightly compact, and the deep staining and pyknosis of the cells were reduced. (Fig. 1)

Noni adjusted neurotransmitters in brain of memory impairment mice. Compare with control group, the Ach, 5-HT, DA, NA in the model group were significantly decreased ($p < 0.01$). Compare with model group, the four neurotransmitters of the Ginseng group, High-dose Noni group and Middle-dose group were significantly regained ($p < 0.01$ or $p < 0.05$). (Table 4)

Table 4

Expression of neurotransmitters in brain($\bar{x}$ ± s,n = 8)

Group	ACh(pmol/g)	5-HT(ng/g)	DA(ng/g)	NA(ng/g)
Control	11.55 ± 0.95	7.31 ± 0.84	25.85 ± 2.96	37.68 ± 8.11
Model	7.86 ± 1.00**	5.03 ± 0.28**	16.10 ± 1.18**	27.39 ± 1.84**
Ginseng	14.70 ± 3.00##	6.75 ± 0.61##	26.72 ± 5.28##	36.40 ± 5.50##
H-Noni	14.72 ± 3.60##	6.79 ± 0.73##	26.40 ± 2.59##	41.00 ± 6.91##
M-Noni	11.18 ± 2.23##	6.06 ± 0.94##	21.06 ± 4.69#	35.46 ± 3.90#
L-Noni	9.77 ± 1.56	5.64 ± 0.44	19.18 ± 3.51	30.26 ± 1.38
Notes: vs. control group **$p < 0.01$; vs. model group #$p < 0.05$, ##$p < 0.01$				

Noni improved anti-oxygen ability in memory impairment mice.

Compare with control group, All the enzymes in the model group were significantly decreased ($p < 0.01$) and MDA in brain were increased significantly ($p < 0.01$). Compare with model group, the Ginseng group and High-dose Noni group regained all the enzymes and decreased the content of MDA. (Table 5)

Table 5

Expression of T-SOD, CuZn-SOD, Mn-SOD, CAT, LPO and MDA in brain($\bar{x}$ ± s,n = 8)

Group	T-SOD (U/mgprot)	CuZn-SOD (U/mgprot)	Mn-SOD (U/mgprot)	CAT (U/mgprot)	LPO (U/mgprot)	MDA (mgprot/ml)
Control	141.37 ± 13.07	19.34 ± 2.39	122.03 ± 11.71	3.94 ± 0.25	0.57 ± 0.13	2.08 ± 0.40
Model	104.96 ± 10.01**	7.09 ± 2.59**	97.87 ± 10.98**	3.29 ± 0.23**	0.27 ± 0.06**	2.58 ± 0.20**
Ginseng	139.41 ± 20.76##	17.18 ± 3.42##	122.23 ± 18.15##	3.70 ± 0.42	0.54 ± 0.09##	2.21 ± 0.42#
H-Noni	141.69 ± 18.19##	19.40 ± 4.69##	122.29 ± 14.85##	4.99 ± 0.66##	0.56 ± 0.11##	1.81 ± 0.38##
M-Noni	111.23 ± 11.71	10.74 ± 3.29#	100.48 ± 8.77	3.71 ± 0.55	0.35 ± 0.12	1.89 ± 0.23##
L-Noni	110.35 ± 14.14	9.43 ± 4.20	100.91 ± 14.93	3.58 ± 0.34	0.32 ± 0.06	2.07 ± 0.23##
Notes: vs. control group **$p < 0.01$; vs. model group #$p < 0.05$, ##$p < 0.01$						

Protein Expression in Brain Tissue of Mice.

In Each Group, Nrf2, KEAP1 and HO-1 protein expressions in the brain were significantly decreased in the model group compared with the normal group ($p < 0.05$ or $p < 0.01$). Compared with the model group, Nrf2, KEAP1 and HO-1 protein expression in the brain was significantly increased in the Ginseng group and high-dose Noni groups ($p < 0.05$ and $p < 0.01$) (Fig. 2).

Discussion

With the development of society, the problem of memory impairment is becoming more and more serious and has gradually become a global problem. It is estimated that 150 million people will suffer from dementia by 2030. At present, there is no specific drug for memory impairment. As a kind of fruit with special functions, Noni has the potential to become a product to improve memory. Our experience shows after 14 days of modeling, there were significant differences between the model group and the control group, which showed the changes of oxidative stress indexes and behavioral changes. After the application of Ginseng or Noni, the overall levels of Nrf2, Keap1 and HO-1 were significantly higher than those of the model group. In addition, Nrf2 was increased and the level of oxidative stress was regulated. Nrf2 activates the transcription and translation of phase II detoxification enzymes, such as SOD, CAT, LPO, and so on. As a result, the expression of these enzymes in the brain tissue is increased and neurotransmitters in brain are also regained, which has a protective effect on the neurons cell. Furthermore, memory impairment has been recovered. The results of HE staining showed that the pyramidal cells of hippocampal CA3 in the model group were loosely arranged and had obvious hyperchromatic or pyknosis. Results indicated that there was obvious neuron loss after hydrocortisone injection. After administration of Ginseng or Noni, the hyperchromic and pyknosis of vertebral cells in CA3 area of hippocampus was alleviated, means that Ginseng or Noni could inhibit the loss of neurons in mice. The behavior results of step-down test and passive avoidance test showed that hydrocortisone induced severe memory impairment in mice. Ginseng or Noni could improve the memory of mice.

Memory is an important function of human brain and its physiological function mainly depends on the hippocampal CA3 area[15]. The structural basis of memory is the limbic system, in which neurons in hippocampal CA3 area are important cells involved in memory function[16]. Pyramidal cells are the main projection neurons in the hippocampus. The number of synapses in pyramidal cells is very large, which is the structural basis of information transmission between neurons[17]. Therefore, pyramidal cells in hippocampal CA3 area are closely related to memory.

Step-down test and passive avoidance test are the most commonly used experimental methods to test the learning and memory of mice. The step-down test takes the latency of staying on the platform and escaping to the platform, as well as the error times of jumping back to the click area as the index to investigate the learning and memory function of mice. Passive avoidance test is an inhibitory avoidance task designed by mice that tend to go dark and avoid light. It reflects the function of hippocampus[18].

Some studies have shown that the decline of memory function in mice may be related to the decrease of CAT and LPO content in brain[19].

The current studies have shown that Nrf2 is involved in different signaling pathways, including Nrf2/HO-1 signaling pathway[20], Keap1/Nrf2 signaling pathway[21], Nrf2/PINK1 mitochondrial signaling pathway[22], Nrf2/MAPK signaling pathway[23], Pi3k/Akt/Nrf2 signaling pathway[24]. Nrf2 involved signaling pathways regulate antioxidant defense system and play an important role in species antioxidant under regulatory conditions Promote defense and even resist more damage. Nrf2 is expressed in various organs of the body and participates in the protection and defense process of various systems of the body. Nrf2/HO-1 signaling pathway is a potential target to prevent memory damage by regulating the redox balance of the brain. Oxidative stress is considered as a sign of memory loss and a risk factor for memory impairment. Exogenous antioxidants can be supplemented to reduce the reaction degree of oxidative stress. Especially, Nrf2 is a good choice to improve the endogenous antioxidant defense strategy pathway. It is a good choice to study the molecular redox balance in cells and master the antioxidants that regulate phase II detoxification. Under physiological conditions, Nrf2 binds to Keap1 in the cytoplasm. When the level of endogenous or exogenous ROS increases, Nrf2 and Keap1 dissociate, and the phosphorylated Nrf2 is transferred to the nucleus, which combines with the small Maf protein in the nucleus to form dimer, which starts the transcription of phase II detoxification enzymes including HO-1, LPO, SOD, CAT and so on. After translation, the intracellular phase II detoxification enzymes increase, accelerating the scavenging and metabolism of ROS can restore the internal environment of cells. HO-1 plays an antioxidant role by removing oxygen free radicals by carbon monoxide and free iron. It can eliminate the memory damage caused by hydrocortisone, inhibit lipid peroxidation on cell membrane, and protect tissue cells from oxidative damage. Noni has been reported it contain Zinc[25]. Zinc is an important element in brain, which has association with memory in mammal. In this study CuZn-SOD decreased after intragastric gavage of hydrocortisone and recovered during intragastric gavage Noni.

Noni can regulate Nrf2/KEAP1/HO-1 signaling pathway protein and affect the synthesis of downstream oxidative stress protein. Noni can reduce the oxidative stress damage of nerve cells and increase the neurotransmitters in brain, which ameliorates the memory impairment induced by hydrocortisone. Noni play a protective role in mice.

Conclusion

Based on these findings, it can be suggested that Noni might be a powerful antioxidant and protect nerve cell. Noni may possess as a potential benefit for the treatment of memory impairment.

Declarations

Ethics and Consent to Participate

This retrospective study was approved by the Ethics Committee of Beijing University of Chinese Medicine (Beijing, China). BUCM-4-20190102-3008.

Consent for publication

Not applicable.

Availability of data and materials

Serum and brain tissue expression profiles and correlation analysis data are available from the corresponding author on reasonable request.

Competing interests

The authors report no conflict of interests.

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Authors' contributions

Conceptualization, JJZ and CW; methodology, YLZ and RYT; validation, JLL and XJH; formal analysis, FZ and CDW; writing—original draft preparation, RZ and SRD; writing—review and editing SXD and SHY. All authors have read and agreed to the published version of the manuscript.

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Figures

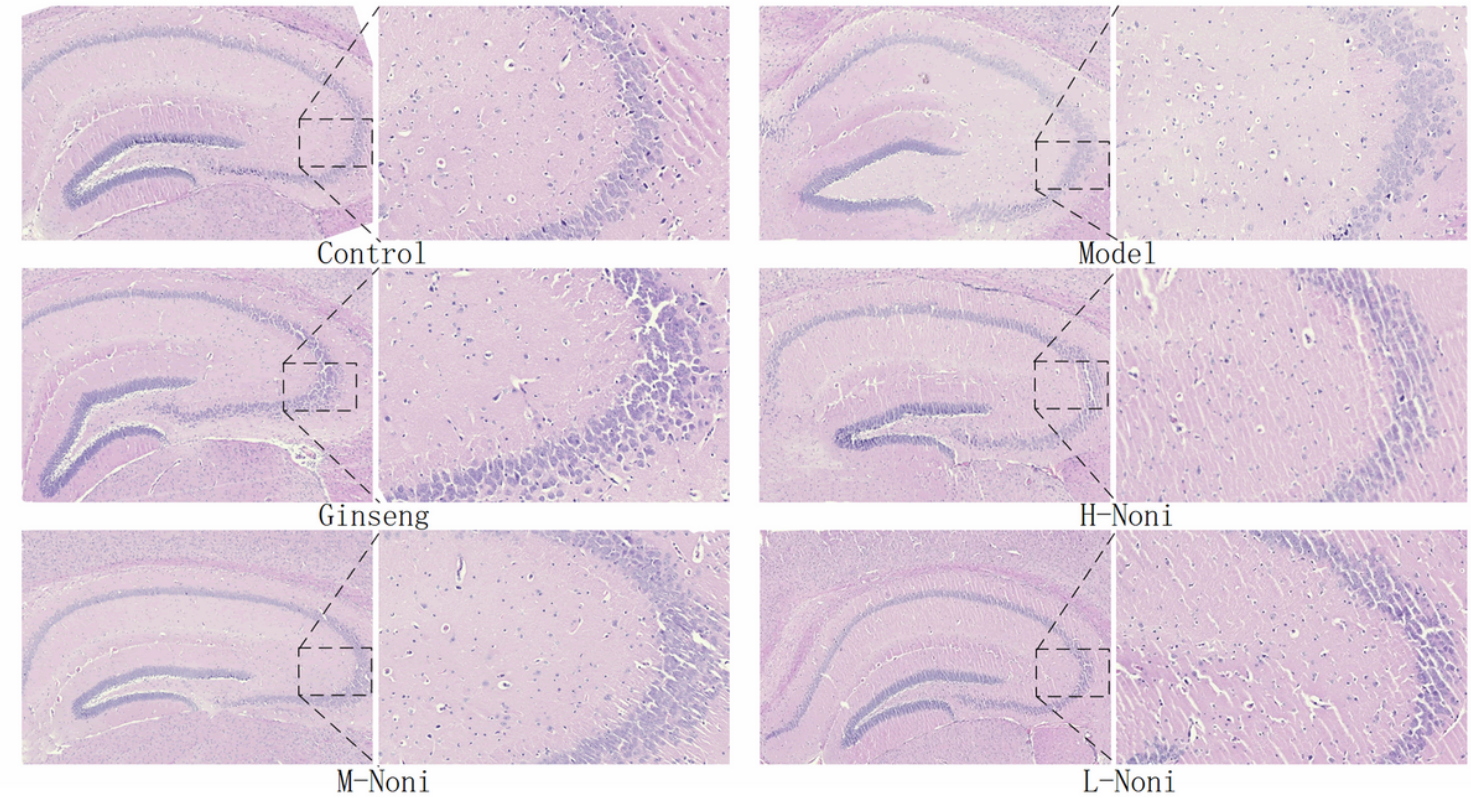

Figure 1

Mice Brain Tissue of HE staining (×10, ×100)

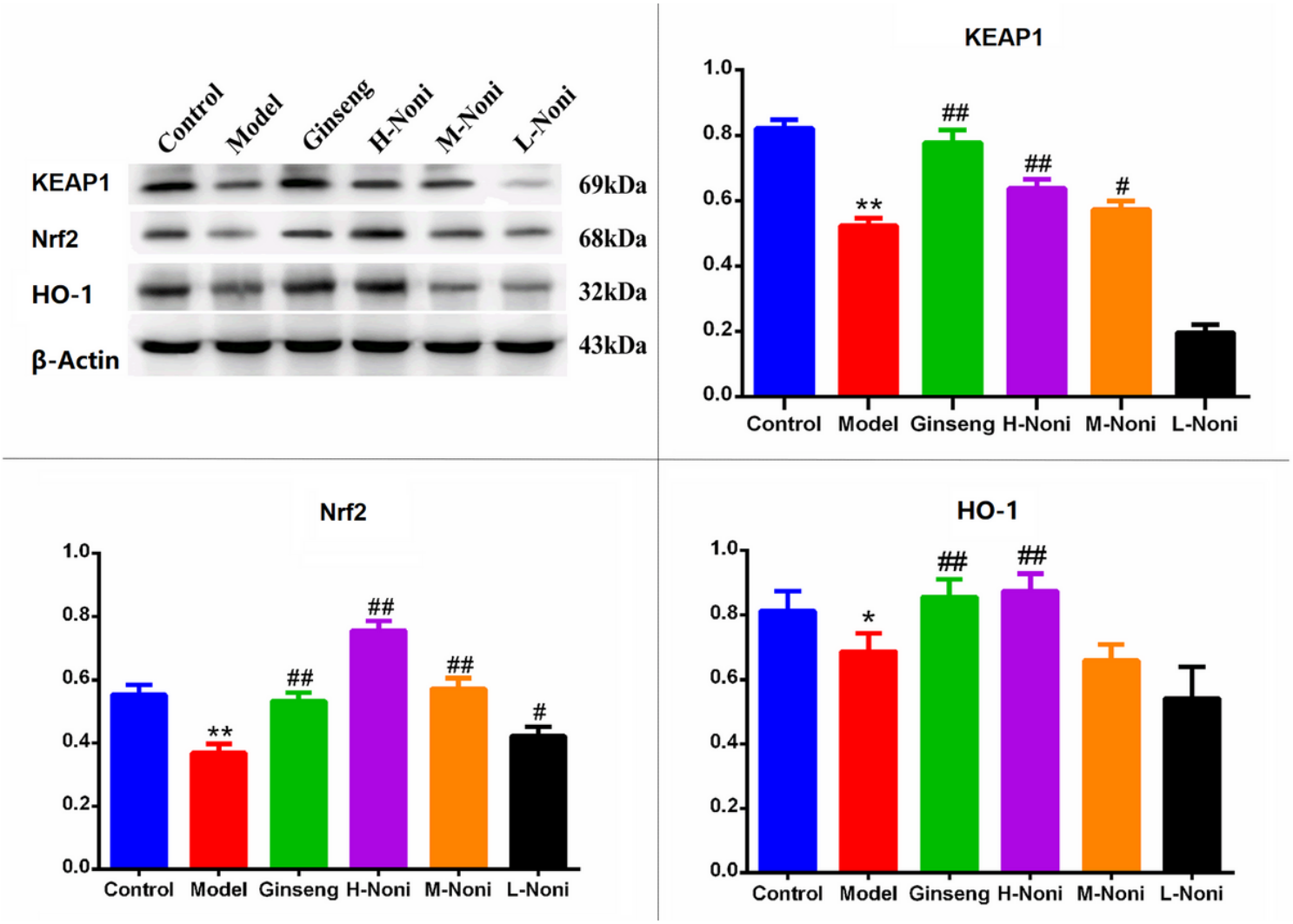

Figure 2

Nrf2, HO-1 and KEAP1 Protein Expression in Brain Tissue of Mice in Each Group ($\bar{x}$±s, n=3) Notes: vs. control group *p<0.05, **p<0.01; vs. model group #p<0.05, ##p<0.01