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·营养与保健·

# 葛仙米对高脂血症小鼠氧化应激的保护作用

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**摘　要:** 大多数与衰老相关的健康问题，如皱纹、心脏病和阿尔茨海默氏症，都是由体内过度的氧化应激引起的。高脂饮食（HFD）引起的高脂血症会导致机体脂质代谢紊乱、氧化应激等，为探究葛仙米对饮食诱导的小鼠高脂血症的保护作用，实验选用 6 周龄 C57BL/6J 雄性小鼠，先喂饲高脂饲料（HFD）4 周，然后在高脂饲料中添加不同剂量的葛仙米饲喂 6 周。结果表明，高脂饮食可导致小鼠高脂血症和明显的血脂异常。高脂饮食中添加葛仙米可降低血清甘油三酯（TG）、总胆固醇（TC）、低密度脂蛋白胆固醇（LDL-C），升高高密度脂蛋白胆固醇（HDL-C），能显著降低肝指数和丙氨酸氨基转移酶（ALT）、天冬氨酸氨基转移酶（AST）活性。2.5% 和 7.5% 葛仙米组小鼠肝组织丙二醛（MDA）含量显著降低，总抗氧化能力（T-AOC）、肝组织超氧化物歧化酶（SOD）和谷胱甘肽（GSH）含量显著升高（$P<0.05$）。此外，葛仙米还能显著增加肝组织低密度脂蛋白受体、CYP7a1 和 LXR-$\alpha$ 的表达（$P<0.05$）。综上，葛仙米对高脂饲料喂养的小鼠具有降脂作用，其机制可能与提高 LDLR 和 CYP7a1 的抗氧化活性及基因表达有关。

**关键词:** 葛仙米, 高脂血症, 小鼠, 氧化应激

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# Protective Effect of *Nostoc sphaeroids* Kütz on Oxidative Stress in Hyperlipidemic Mice

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**Abstract:** Most health problems associated with aging, such as wrinkles, heart disease and Alzheimer's disease were caused by excessive oxidative stress in the body. Hyperlipidemia caused by high-fat diet(HFD) would lead to lipid metabolism disorder, oxidative stress and so on. The purpose of this study was to investigate the protective effect of *Nostoc sphaeroids* Kütz(NSK) on diet-induced hyperlipidemia in mice. In the experiment, six-week-old C57BL/6j male mice were fed with high-fat diet(HFD) for 4 weeks, and then fed with high-fat diet supplemented with different doses of NSK for 6 weeks. Results showed that: High-fat diet could lead to hyperlipidemia and obvious dyslipidemia in mice. The addition of NSK to high-fat diet decreased serum triglyceride(TG), serum total cholesterol(TC), low density lipid cholesterol(LDL-C), while high density lipid cholesterol(HDL-C) increased significantly($P<0.05$). It could also significantly reduce the liver index and the enzyme activities of alanine transaminase(ALT) and aspartate transaminase(AST). Through the results of this experiment, it was found that the level of malondialdehyde (MDA) in the liver tissue of 2.5% and 7.5% NSK group decreased, while total antioxidant capacity(T-AOC), hepatic superoxide dismutase(SOD) and glutathione(GSH) increased, and the difference was statistically significant($P<0.05$). Furthermore, the expression of LDLR,CYP7a1 and LXR-$\alpha$ in liver tissue of mice supplemented with NSK in HFD significantly increased($P<0.05$). In conclusion, NSK hadlipid-lowering effect on HFD-fed mice and it might be related to increase the antioxidant activity and gene expression of LDLR and

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CYP7a1.

**Key words:** *Nostoc sphaeroids* Kütz; hyperlipidemia; mice; oxidative stress

With the development of society, the incidence of cardiovascular and cerebrovascular diseases is getting higher and higher. Cardio-cerebrovascular disease is one of the main chronic diseases in modern society. Hyperlipidemia caused by high-fat diet is the main inducement for the development of cardio-cerebrovascular diseases[1−3]. There is an important relationship between human health, metabolism and diet. However, excessive food consumption may lead to obesity and hyperlipidemia, especially high-fat diets or high sugar diets[4−6]. In particular, hyperlipidemia caused by high-fat diet (HFD) will lead to lipid metabolism disorder and so on[7−11]. Research have showed that HFD-fed mice may induce serious oxidative stress[12−14]. Increased production of free radicals and decreased enzymatic and nonenzymatic antioxidants are the main features of oxidative stress. Dyslipidemia/hypercholesterolemia accumulation in endothelial cells, hepatocytes, leukocytes, erythrocytes, and platelets provokes the production of reactive oxygen species (ROS) and reduces antioxidant defenses. This can lead to redox imbalance, oxidative stress, and metabolic alterations[15−18].

Cyanobacteria(BGA) have been living on the earth for thousands of years, and are often used as food and medicine in Asian countries, especially China. Species such as *Nostoc flagelliforme* Born., *Spirulina platensis*, and *Nostoc sphaeroides* Kütz (NSK) contain a wide range of bioactive compounds and have various functions[19−21].One of the most intriguing BGA species is NSK, also known as Ge-Xian-Mi in China, which has been used to promote health for centuries. According to the literature review, *Nostoc sphaeroides* Kütz contains polysaccharides, proteins, vitamins, and a variety of essential amino acids, especially high contents of polysaccharides and protein. In addition, it also has biological functions such as regulating dyslipidemia, anti-cancer, anti-diabetes, anti-virus and anti-inflammation[19,22−23]. Studies in our laboratory showed that *Nostoc sphaeroides* Kütz could significantly improve the dyslipidemia caused by high-fat diet in male C57BL/6j mice, and might have a certain potential value in reducing atherosclerosis[24]. Nevertheless, it remained unknown whether *Nostoc sphaeroides* Kütz could have effect on oxidative stress or regulatory effects on liver lipid accumulation in HFD-fed mice. Therefore, it was important to investigate the lipid-lowering mechanisms of *Nostoc sphaeroides* Kütz(NSK). Our study aimed to clarify its protective effect on hyperlipidemia-induced oxidative stressas by evaluated gene expressions of LDLR and CYP7a1 in mice's liver.

## 1 Materials and Methods

### 1.1 Materials and instruments

SPF C57BL/6j mice male, 6 weeks old, 60 mice,were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd. (Beijing, China), The license number (Beijing) 2012-0031; Feeds were provided by Beijing Keao Xieli Feed Co., Ltd. (Beijing, China); Powdered *Nostoc sphaeroides* Kütz(NSK) after being superfinely pulverized at −20 °C for 2 hours, the dried *Nostoc sphaeroides* Kütz(NSK) was passed through a 20-mesh sieve, the experimental sample was provided by Hunan Yandi Biological Engineering Co., Ltd., the main components of *Nostoc sphaeroides* Kütz were 47.3% polysaccharides, 30.8% protein, 5.7% ash and 5.6% water, and the rest were minerals and vitamins, and compundswere identified by Societe Generale de Surveillance S.A. (Shanghai, China); Assay kits for total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), alanine transaminase (ALT), aspartate transaminase (AST) were from Nanjing Jiancheng Bioengineering Institute; Total RNA extraction regent, SYBR Green Master primer, and oligo (dT)18 were obtained from Roche.

JJ-12J Dehydrator, JB-P5 Embedding Machine Wuhan Junjie Electronics Co., Ltd.; RM2016 Pathology Microtome Shanghai Leica Instruments Co., Ltd.; JB-L5 Freeze Table Wuhan Junjie Electronics Co., Ltd.; KD-P tissue spreading Machine Zhejiang Jinhua Kedi Instrument Equipment Co., Ltd.; NIKON ECLIPSE E100 upright optical microscope Nikon, Japan.

### 1.2 Experimental Methods

1.2.1 Mice treatment The surgical procedures of experimental animals were in accordance with the approval of the Animal Ethics Committee of Beijing Union University. The 40 male C57BL/6j mice, aged 6 weeks. The mice were raised in a SPF animal room with a temperature of (22±2) ℃ and a humidity of

about 50% in a 12-hour bright/dark cycle environment. After 7 days of adaptive feeding, the mice were randomly divided into four groups (n=10 in each group, one animal per cage): Control group, HFD group, 2.5% NSK group and 7.5% NSK group. All were raised separately in a separate cage. The mice in the control group were treated with AIN-93M-controlled diet, while the HFD group, the 2.5% NSK group, and the 7.5% NSK group were treated with a modified high-fat diet(HFD) based on AIN-93M for 4 weeks. In the following 6 weeks, the control mice continued to be fed with the control diet, the HFD group was treated with an HFD, the 2.5% NSK group was treated with an HFD supplemented with 2.5% NSK(w/w, 2.5% NSK), and the 7.5% NSK group was treated with HFD supplemented with 7.5% NSK(w/w, 7.5% NSK). The dietary ingredients are shown in Table 1. The total kilocalorie of HFD, 2.5% NSK, 7.5% NSK was 5150, 5140, and 5214 kcal respectively, and the dietary calories between the HFD-fed groups were basically the same. Four weeks later, the blood samples were collected through retroorbital hemorrhage and transferred into the centrifuge tube. After 40 minutes of rest, the serum samples were obtained by centrifugation at 4 ℃ and 4000 r/min for 10 minutes. The serum samples were stored at −80 ℃ for further analysis. The mice were given 16 hours of fasting before they were killed. The mice were weighed at 9:00 a.m the next day and then anesthetized by intraperitoneal injection of barbital. Blood samples taken from the orbital vein puncture. Liver tissues were collected and stored at −80 ℃, then subjected to real-time quantitative reverse transcription polymerase chain reaction (qRT–PCR) analysis.

Table 1 Composition of assay diets

| Ingredient (g) | Control diet | HFD | NSK (2.5%) | NSK (7.5%) |
|---|---|---|---|---|
| Cornstarch | 465.7 | 235.7 | 233.2 | 228.2 |
| Casein | 140 | 110 | 110 | 110 |
| Dextrinized cornstarch | 155 | 155 | 155 | 155 |
| Sucrose | 100 | 100 | 100 | 100 |
| Soybean oil | 40 | 40 | 40 | 40 |
| Choline bitartrate | 2.5 | 2.5 | 2.5 | 2.5 |
| Fiber[1] | 50 | 50 | 50 | 50 |
| Mineral mix[2] | 35 | 35 | 35 | 35 |
| Vitamin mix[3] | 10 | 10 | 10 | 10 |
| L-Cysteine | 1.8 | 1.8 | 1.8 | 1.8 |
| Lard | 0 | 150 | 150 | 150 |
| Cholesterol | 0 | 10 | 10 | 10 |
| yolk | 0 | 100 | 100 | 100 |
| NSK powder | 0 | 0 | 25 | 75 |

Note:1: Solka-Floc cellulose. 2: AIN-93 mineral mix. 3: AIN-93 vitamin.

1.2.2 Biochemical analysis in serum The determination of lipids in serum was as mentioned earlier[25]. The concentrations of serum total cholesterol, triglyceride, HDL and LDL were tested by commercial kit. Concentrations of AST and ALT enzyme activity in serum were measured by commercial assay kits. All the procedures were followed by the instructions of commercial assay kits.

1.2.3 Effect of NSK on antioxidants in liver The levels of T-AOC, SOD, GSH and MDA in liver were determined by the assay kits. All the procedures were followed by the instructions of commercial assay kits.

1.2.4 Determination of LDLR, CYP7a1 and LXR-$\alpha$ gene expression in liver Total RNA from mice liver issues was extracted using a total RNA extraction kitaccording to the manufacturer 's protocol. Two micrograms of total RNA samples were used to synthesize cDNA using the revert aid first strand cDNA synthesis kit. Quantitative real-time reverse-transcription PCR (qRT−PCR) was performed in triplicate using SYBR Green and a LightCycler 480 Real-Time PCR System (Roche Diagnostics). Each well was loaded with a 20 μL sample, containing 2.5 μL cDNA, 2.0 μL target primers, 8.0 μL water, and 12.5 μL Kapa SYBR Fast Master Mix. Hot-start PCR was performed for 40 cycles. Each cycle consisted of denaturation for 15 s at 95 ℃, annealing for 30 s and elongation for 30 s at 60 ℃. Roche Light Cycler software (version 1.5.0, Roche Diagnostics) was utilized for data analysis. The results were analyzed using the $2^{-\Delta\Delta Ct}$ method of analysis. Mean expression levels for control group mice were set as 100%. The primers used are shown in Table 2.

Table 2 Primer pairs used for the real-time quantitative PCR analysis

| Genbank ID | Gene Name | Primer Sequence (5' to 3') |
|---|---|---|
| NM_007393.3 | $\beta$-actin | GTGACGTTGACATCCGTAAAGA |
| | | GTAACAGTCCGCCTAGAAGCAC |
| NM_001252658.1 | LDLR | ATTCAGTCCCAGGCAGCGTATC |
| | | TTCTTGATCTTGGCGGGTGTTC |
| NM_001278601.1 | CYP7a1 | GGGGATTGCTGTGGTAGTGAG |
| | | CAGGGAGTTTGTGATGAAGTGG |
| NM_001177730.1 | LXR-$\alpha$ | CCCACGACCCACTGATGTTC |
| | | CACAAAGGACACGGTGAAACA |

## 1.3 Statistical analysis

Results were represented as the mean±SEM. One-way analysis of variance (ANOVA) and Newman-Keuls post hoc tests were performed to compare differences between groups by using SPSS version 22.0. $P<0.05$ was considered statistically significant.

## 2 Results and Analysis

### 2.1 Effect of NSK on body weight and food utilization rate

The body weight and food utilization rate of mice in each group of were monitored every week. The weight of the animals increased significantly after the first 4 weeks of feeding. The growth curve of 10 weeks is shown in Fig.1a~Fig.1b. The weight of mice fed with HFD for 10 week was significantly increased ($P$<0.05), while that of mice supplemented with NSK decreased the weight gain caused by HFD (Fig.1a~Fig.1b). Mean daily food utilization rate were shown in Fig.1c~Fig.1d. Feeding during 1~4 weeks, the food utilization rate of the HFD group, the 2.5% NSK group as well as 7.5% NSK group was higher than that of the control group, the difference was statistically significant ($P$<0.05), and there was no significant difference in food utilization rate between the HFD group, the 2.5% NSK group, and the 7.5% NSK group. In the following 6 weeks, the food utilization rate of the 2.5% NSK group and the 7.5% NSK group were significantly lower than that of the HFD group, and there was no significant difference between the 2.5% NSK group and the 7.5% NSK group.

### 2.2 Effect of NSK on serum lipids

The effects of NSK on serum lipid levels of TG, TC, LDL and HDL were investigated. Feeding during 1~4 weeks, the levels of serum lipids the HFD group, the 2.5% NSK group as well as 7.5% NSK group was significantly higher than that of the control group ($P$<0.05). The results showed that the animal model of hyperlipidemia was established successfully. In the following 6 weeks, compared with the HFD group, the TC, TG, LDL level of the NSK group was significantly lower, while the HDL level was significantly higher, especially in the 7.5% NSK group (Fig.2).

### 2.3 Effect of NSK on liver injury in mice with HFD

Compared with the control group, the mice in HFD group had increased liver index. NSK supplementation significantly reduced liver index of mice compared with HFD group (Table 3). HFD feed caused a significant rise in serum ALT and AST enzyme activity, and NSK supplementation dramatically reduced the theenzyme activity of ALT and AST, especially in 7.5% NSK group (Fig.3a~Fig.3b). The results indicated that NSK have beneficial in liver function.

### 2.4 Effect of NSK on antioxidants in liver

Evaluation of the effect of high fat diet inexperimental mice showed a significant reduction in T-AOC, SOD and GSH in HFD-fed mice compared to the control group (Fig.4a~Fig.4c) ($P$<0.05), while

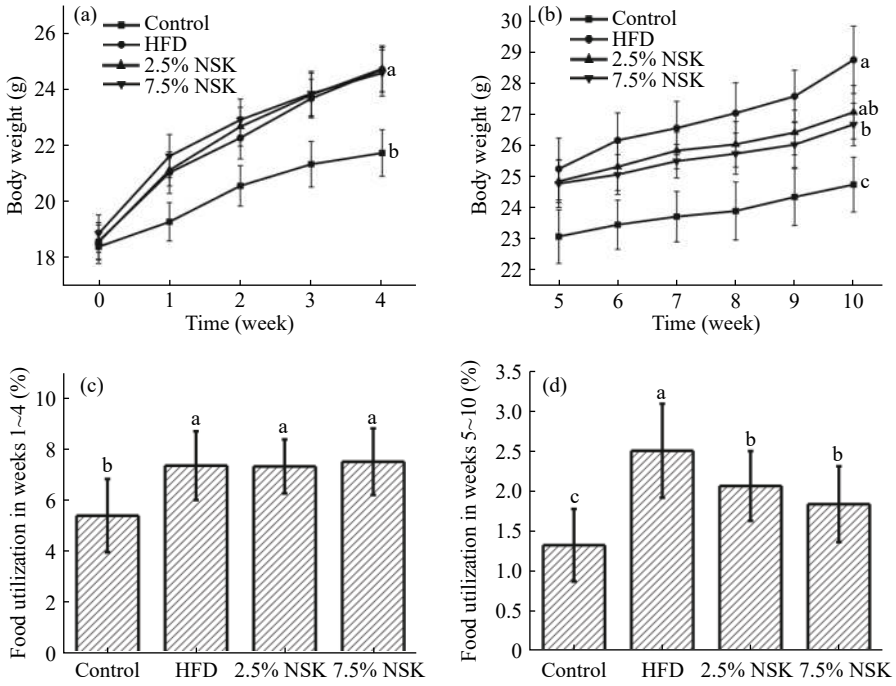


Fig.1 Body weight and food utilization rate

Notes: (a). Body weight during modeling; (b). Body weight during NSK intervation; (c). Food utilization rate during modeling; (d). Food utilization rate during NSK intervation (Food utilization rate (%) = $\frac{\text{Food intake of mice (g)}}{\text{Mouse weight gain (g)}} \times 100$). Bars marked with different letters represent statistically significant ($P$<0.05), whereas bars labeled with the same letter indicate no statistically significant difference between the groups ($P$>0.05).

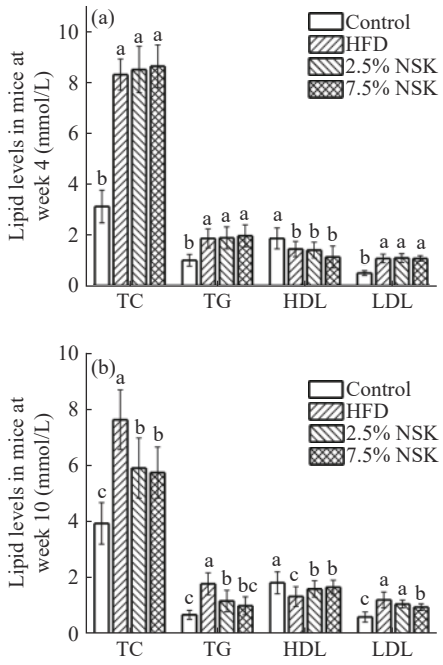


Fig.2 Effects of NSK on lipid levels in serum

Notes: (a).Lipid levels at week 1~4 , (b). Lipid levels at week 5~10; Values represent mean±SEM; n=10 in each group. Bars marked with different letters represent statistically significant ($P$<0.05), whereas bars labeled with the same letter indicate no statistically significant difference between the groups ($P$>0.05).

treatment with NSK at a dose of 7.5% significantly increased the T-AOC, SOD and GSH ($P$<0.05). In addition, after HFD feeding for 10 weeks, compared with the control group, the liver MDA of the model group increased significantly, while the liver MDA of the NSK dose group decreased significantly (Fig.4d). These results suggested that NSK has beneficial effects in mice liver oxidative damage induced by HFD.

### 2.5 Effect of NSK on gene expression of LDLR, CYP7a1, and LXR-$\alpha$

Compared with the control group, the gene expressions of LDLR and CYP7a1in HFD group were significant decrease, while gene expressions of LDLR and CYP7a1 in two NSK groups increased significantly compared to the mices in the HFD group ($P$<0.05), especially, the gene expressions in 7.5% NSK group were higher than 2.5% NSK group (Fig.5a~Fig.5b). 7.5% NSK group showed a significant increase in the gene expressions of LXR-$\alpha$, but no significant difference in other groups (Fig.5c).

## 3 Discussion

Dyslipidemia is a lipid metabolism disorder which may induce different diseases, such as atherosclerosis, metabolic syndrome, hypertension and cardiovascular disease. Due to people's increasing awareness of health management, there has been an

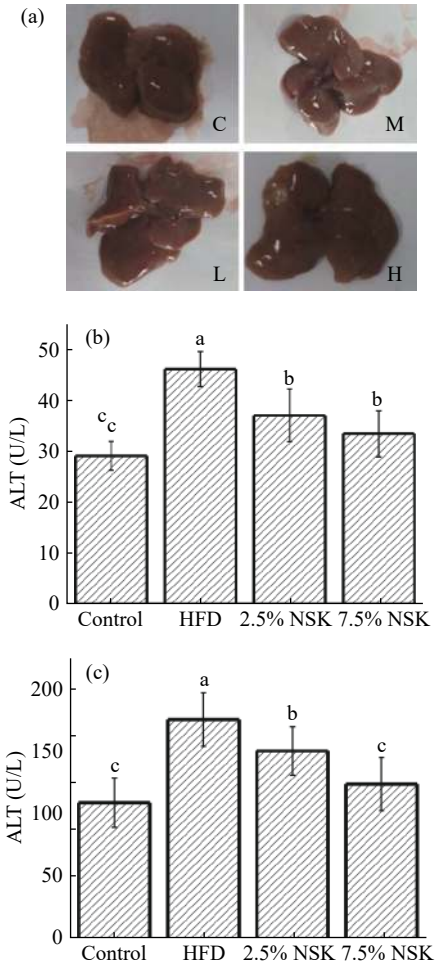


Fig.3 Effects of NSK on liver injury in mice with high-fat die

Notes: (a). Typical liver morphological images, C: Control, M: HFD, L:NSK (2.5%), H: NSK (7.5%); (b). ALT in serum; (c). AST in serum. Bars marked with different letters represent statistically significant ($P$<0.05), whereas bars labeled with the same letter indicate no statistically significant difference between the groups ($P$>0.05).

Table 3 Effect of *Nostoc sphaeroides* Kütz on liver index of mice

| Dose | animals | body weight | liver weight | Liver index(%) |
|---|---|---|---|---|
| Control | 10 | 24.73±0.88$^{c}$ | 0.86±0.27$^{c}$ | 3.45±0.94$^{d}$ |
| HFD | 10 | 28.73±1.08a | 1.63±0.39$^{a}$ | 5.53±1.02$^{a}$ |
| 2.5%NSK | 10 | 27.05±0.86$^{ab}$ | 1.53±0.42$^{a}$ | 5.16±1.37$^{ab}$ |
| 7.5%NSK | 10 | 26.26±0.61$^{b}$ | 1.25±0.34$^{b}$ | 4.66±0.96$^{bc}$ |

Notes: Values represent mean±SEM; n=10 in each group. Superscript letters represent statistically significant differences ($P$<0.05). Instances of the same letter between groups indicate that no statistically significant difference was found ($P$>0.05).

increasing demand for using safe and effective natural products as preventive agents against dyslipidemia[5,26−28]. The increase of TC, TG, LDL and decrease of HDL in serum are the common features of dyslipidemia. Dyslipidemia can accelerate the development of atherosclerosis and cardiovascular disease, which are the main causes of death [29−31].

In the past few years, our laboratory had done a lot of work in the improvement of dyslipidemia with

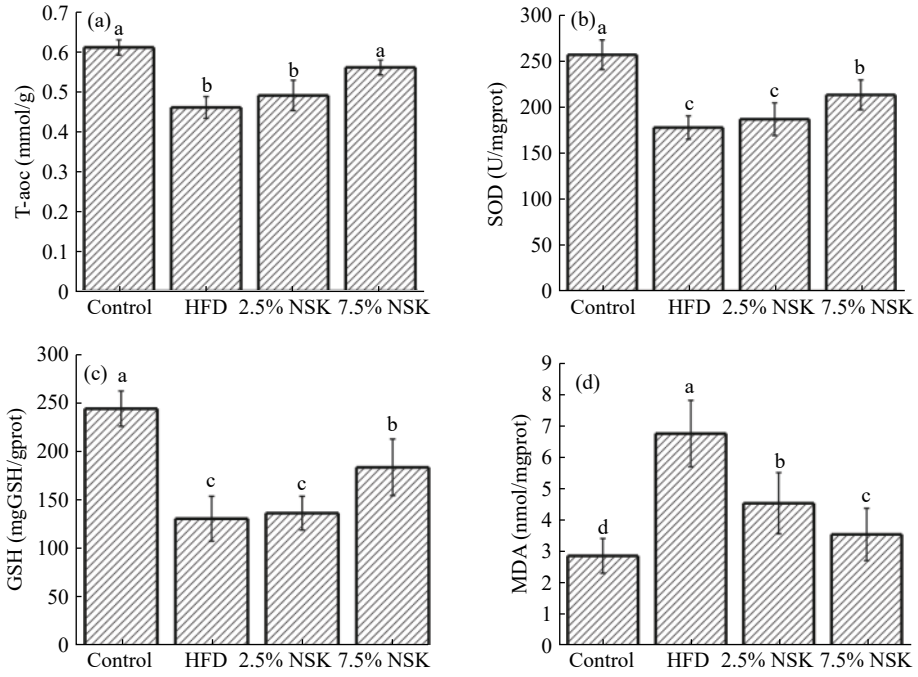


Fig.4　Effect of NSK on lipid peroxidation and antioxidants in liver

Notes: (a).The concentration of T-AOC in liver; (b). The enzyme activity of SOD in liver; (c). The concentration of GSH in liver; (d). The concentration of MDA in liver; Values represent mean±SEM, n=10 in each group;Bars marked with different letters represent statistically significant ($P$<0.05), whereas bars labeled with the same letter indicate no statistically significant difference between the groups ($P$>0.05).

NSK. On the one hand, we found that NSK has beneficial effects for the HFD-fed mice. NSK decreased the levels of TC, TG, LDL in serum, and ameliorated inflammation in the HFD-fed mice. The beneficial effects were primarily attributed to the suppression of FAS and SREBP-1 protein expression, and the inhibition of TNF-$\alpha$, IL-1$\beta$, IL-6, and NF-kB gene expression[24]. On the other hand, we found that hyperlipidemia was associated with chronic inflammation and intestinal dysbiosis. NSK significantly ameliorated hyperlipidemia induced by a HFD in mice, potentially via a decrease intestinal inflammation, increase in intestinal barrier integrity, and amelioration in the gut microbiota[31].

Although previous research had reported that NSK lowers plasma lipid and produces beneficial effects in mice, the effects of this nostoc on liver lipid metabolism and liver oxidative stress had not been investigated. There has been very limited understanding of its mechanisms. In the present study, we used a high-fat diet mouse model to study the beneficial effects of NSK treatment on serum lipids, liver lipid metabolism and liver oxidative stress. In our study, the mice were received HFD feeding supplemented with 0%, 2.5%, 7.5% NSK for 6 weeks. HFD-fed mice showed significantly increase in body weight and food utilization rate, supplementation with NSK significantly decreased body weight gain and food utilization rate induced by HFD-fed. HFD-fed mice showed a significant increase in the serum contents of TC, TG, and LDL, while decreases in the serum contents of HDL, compared with mice in the control group. In contrast, HFD-fed mice supplemented with NSK significant get better by observing several indicators inserum. These results were in accordance with the results of a previous study by Chai et al[20]. Furthermore, HFD-fed mice showed a significant increase in liver index, and the color of liver was lighter, compared with control group. HFD feed caused a significant rise in serum ALT and AST, and NSK supplementation reduced the enzyme activity of ALT and AST dramatically, especially in 7.5% NSK group. The results indicated that NSK had beneficial in liver function. It was consistent with a previous study performed by Ke et al[32]. Many mediators and enzymes were involved in the regulation of liver lipid homeostasis. LDLR, CYP7a1 and LXR-$\alpha$ are important influencing factors in the process of lipid metabolism. We investigated the gene expression of these three mediators in liver by using Rt-PCR. The results of this study showed that the expression of LDLR, CYP7a1 and LXR-$\alpha$ in mouse liver increased with the addition of NSK to HFD, and the gene expression increased with the dose. The disorder of

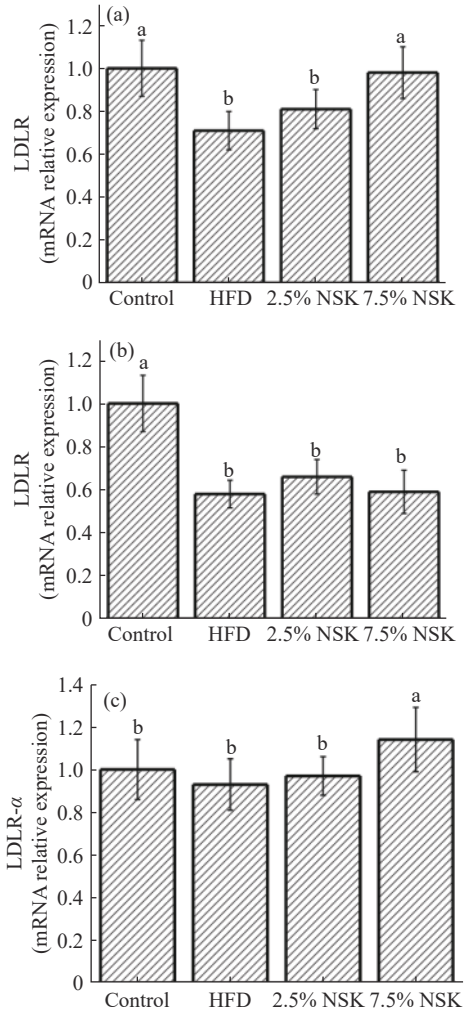


Fig.5 Effect of NSK on liver mRNA expression in mice

Notes: Bars marked with different letters represent statistically significant ($P$<0.05), whereas bars labeled with the same letter indicate no statistically significant difference between the groups ($P$>0.05).

lipid metabolism could be regulated by dietary intervention, while NSK may play a role by regulating LDLR, CYP7a1. Previous research had shown that long-term high-fat diets could induce oxidative stress. In addition, oxidative stress was one of the mechanisms through hyperlipidemia induced tissue damage[33−34]. Compared with the control group, the T-AOC, SOD and GSH of the mice fed with high fat diet decreased significantly and the MDA increased significantly ($P$<0.05), which led to the abnormal level of lipid peroxidation and the antioxidant defense ability of the liver of mice. Oxidative stress might be caused by the increasing of lipid peroxidation and the decrease of antioxidant defense ability in hyperlipidemia caused by dietary imbalance. Long-term oxidative stress can deplete fatty acids in the liver of patients with hyperlipidemia, promote hepatic steatosis, and lead to tissue cell damage and death. Compared with HFD group, mice fed with HFD supplemented with NSK significantly decreased the level of MDA and increased T-AOC, SOD and GSH in liver tissue ($P$<0.05). From these experimental results, we could see that NSK could improve hyperlipidemia to some extent and had a certain antioxidant capacity to oxidative stress caused by hyperlipidemia.

Hyperlipidemia is a pathological state of lipid metabolism disorder due to various reasons, and it is related to a variety of influencing factors, including diet and genetics. In recent years, the pathogenesis of hyperlipidemia had been explored. In addition to inflammatory factors, intestinal flora and oxidative stress, it might also be related to endoplasmic reticulum stress and gene polymorphism. To further understand the improvement effect of *Nostoc sphaeroides* Kützon hyperlipidemia, we need to conduct more in-depth exploration.

## 4 Conclusions

In conclusion, the NSK had a certain role in reducing blood lipids, and had an effect on mice fed with HFD. The NSK significantly decreased body weight gain induced by high fat diets and ameliorated serum lipids. Furthermore, the addition of NSK to HFD enhanced the antioxidant defense ability of the liver of hyperlipidemic mice. Its mechanism might be that the lipid-lowering effect of NSK was partly mediated by increasing the expression of LDLR, CYP7a1 in the liver. However, the lipid-lowering mechanism and antioxidant effect of NSK need to be further studied.

## 参考文献

[1] Hoyt C L, Burnette J L, Auster-Gussman L. “Obesity is a disease”: Examining the self-regulatory impact of this public-health message[J]. Psychological Science, 2014, 25(4): 997−1002.

[2] Bin-Jumah M N. Monolluma quadrangula protects against oxidative stress and modulates LDL receptor and fatty acid synthase gene expression in hypercholesterolemic rats[J]. Oxidative Medicine and Cellular Longevity, 2018, 2018: 1−10.

[3] Lee K S, Chun S Y, Kwon Y S, et al. Deep sea water improves hypercholesterolemia and hepatic lipid accumulation through the regulation of hepatic lipid metabolic gene expression[J]. Molecular Medicine Reports, 2017, 15(5): 2814−2822.

[4] Daveri E, Cremonini E, Mastaloudis A, et al. Cyanidin and delphinidin modulate inflammation and altered redox signaling improving insulin resistance in high fat-fed mice[J]. Redox Biology, 2018, 18: 16−24.

[5] Xu M X, Wang M, Yang W W. Gold-quercetin nanoparticles prevent metabolic endotoxemia-induced kidney injury by regulating TLR4/NF-kappaB signaling and Nrf2 pathway in high fat diet fed mice[J]. International Journal of Nanomedicine, 2017, 12: 327−345.

[6] Buckman L B, Hasty A H, Flaherty D K, et al. Obesity

induced by a high-fat diet is associated with increased immune cell entry into the central nervous system[J]. Brain Behavior and Immunity, 2014, 35: 33−42.
[7] Agrimi J, Spalletti C, Baroni C, et al. Obese mice exposed to psychosocial stress display cardiac and hippocampal dysfunction associated with local brain-derived neurotrophic factor depletion[J]. EBioMedicine, 2019, 47: 384−401.
[8] Kuang W, Zhang X, Lan Z. Flavonoids extracted from *Linaria vulgaris* protect against hyperlipidemia and hepatic steatosis induced by western-type diet in mice[J]. Archives of Pharmacal Research, 2018, 41(12): 1190−1198.
[9] La Frano M R, Hernandez-Carretero A, Weber N, et al. Diet-induced obesity and weight loss alter bile acid concentrations and bile acid-sensitive gene expression in insulin target tissues of C57BL/6J mice[J]. Nutrition Research, 2017, 46: 11−21.
[10] Miyamoto J, Igarashi M, Watanabe K, et al. Gut microbiota confers host resistance to obesity by metabolizing dietary polyunsaturated fatty acids[J]. Nature Communications, 2019, 10(1): 4007−4015.
[11] Al-Rejaie S S, Aleisa A M, Sayed-Ahmed M M, et al. Protective effect of rutin on the antioxidant genes expression in hypercholestrolemic male Westar rat[J]. BMC Complementary and Alternative Medicine, 2013, 13(1): 136.
[12] Förstermann U. Oxidative stress in vascular disease: Causes, defense mechanisms and potential therapies[J]. Nature Clinical Practice Cardiovascular Medicine, 2008, 5(6): 338−349.
[13] Alcala M, Calderon-Dominguez M, Bustos E, et al. Increased inflammation, oxidative stress and mitochondrial respiration in brown adipose tissue from obese mice[J]. Scientific Reports, 2017, 7(1): 16082.
[14] Seifried H E, Anderson D E, Fisher E I, et al. A review of the interaction among dietary antioxidants and reactive oxygen species[J]. Journal of Nutritional Biochemistry, 2007, 18(9): 567−579.
[15] Schulz M D, Atay C, Heringer J, et al. High-fat-diet-mediated dysbiosis promotes intestinal carcinogenesis independently of obesity[J]. Nature, 2014, 514(7523): 508−512.
[16] Beyaz S, Mana M D, Roper J, et al. High-fat diet enhances stemness and tumorigenicity of intestinal progenitors[J]. Nature, 2016, 531(7592): 53−58.
[17] Zalewska A, Maciejczyk M, Szulimowska J, et al. High-Fat diet affects ceramide content, disturbs mitochondrial redox balance, and induces apoptosis in the submandibular glands of mice[J]. Biomolecules, 2019, 9(12): 877.
[18] Rosas-Villegas A, Sánchez-Tapia M, Avila-Nava A, et al. Differential effect of sucrose and fructose in combination with a high fat diet on intestinal microbiota and kidney oxidative stress[J]. Nutrients, 2017, 9(4): 393.
[19] Johnson H E, King S R, Banack S A, et al. Cyanobacteria (*Nostoc commune*) used as a dietary item in the peruvian highlands produce the neurotoxic amino acid BMAA[J]. Journal of Ethnopharmacology, 2008, 118(1): 159−165.
[20] Ku C S, Kim B, Pham T X, et al. Blue-Green algae inhibit the development of atherosclerotic lesions in apolipoprotein E knockout mice[J]. Journal of Medicinal Food, 2015, 18(12): 1299−1306.
[21] Locati M, Mantovani A, Sica A. Macrophage activation and polarization as an adaptive component of innate immunity[J]. Advances in Immunology, 2013, 120: 163−184.
[22] Li H, Su L, Chen S, et al. Physicochemical characterization and functional analysis of the polysaccharide from the edible microalga nostoc sphaeroides[J]. Molecules, 2018, 23(2): 508.
[23] Guo M, Ding G B, Guo S, et al. Isolation and antitumor efficacy evaluation of a polysaccharide from *Nostoc commune* Vauch[J]. Food & Function, 2015, 6(9): 3035−3044.
[24] Wei F, Liu Y, Bi C, et al. *Nostoc sphaeroids* Kütz powder ameliorates diet-induced hyperlipidemia in C57BL/6j mice[J]. Food & Nutrition Research, 2019, 63: 3618.
[25] Kang H J, Pichiah P B T, Abinaya R V, et al. Hypocholesterolemic effect of quercetin-rich onion peel extract in C57BL/6J mice fed with high cholesterol diet[J]. Food Science & Biotechnology, 2016, 25(3): 855−860.
[26] Yang G, Lee H E, Lee J Y. A pharmacological inhibitor of NLRP3 inflammasome prevents non-alcoholic fatty liver disease in a mouse model induced by high fat diet[J]. Scientific Reports, 2016, 6(1): 24399.
[27] Li L, Zhao Z, Xia J, et al. A long-term high-fat/high-sucrose diet promotes kidney lipid deposition and causes apoptosis and glomerular hypertrophy in bama minipigs[J]. PLoS One, 2015, 10(11): e142884.
[28] Zhai X, Lin D, Zhao Y, et al. Effects of dietary fiber supplementation on fatty acid metabolism and intestinal microbiota diversity in C57BL/6J mice fed with a high-fat diet[J]. Journal of Agricultural and Food Chemistry, 2018, 66(48): 12706−12718.
[29] Petrov P D, García Mediavilla M V, Guzmán C, et al. A network involving gut microbiota, circulating bile acids, and hepatic metabolism genes that protects against non-alcoholic fatty liver disease[J]. Molecular Nutrition & Food Research, 2019, 63(20): e1900487.
[30] Mueller K M, Hartmann K, Kaltenecker D, et al. Adipocyte glucocorticoid receptor deficiency attenuates aging-and HFD-induced obesity and impairs the Feeding-Fasting transition[J]. Diabetes, 2017, 66(2): 272−286.
[31] Wei F, Liu Y, Bi C, et al. *Nostoc sphaeroids* Kütz ameliorates hyperlipidemia and maintains the intestinal barrier and gut microbiota composition of high-fat diet mice[J]. Food ence& Nutrition, 2020, 8(4): 2348−2359.
[32] Ke W, Wang P, Wang X, et al. Dietary Platycodon grandiflorus attenuates hepatic insulin resistance and oxidative stress in high-fat-diet induced non-alcoholic fatty liver disease[J]. Nutrients, 2020, 12(2): 480.
[33] Zilu S, Qian H, Haibin W, et al. Effects of XIAP on high fat diet-induced hepatic steatosis: A mechanism involving NLRP3 inflammasome and oxidative stress[J]. Aging, 2019, 11(24): 12177−12201.
[34] Wang Z, Komatsu T, Ohata Y, et al. Effects of rikkunshito supplementation on resistance to oxidative stress and lifespan in mice[J]. Geriatrics & Gerontology International, 2019, 20(3): 238−247.