Received: 19 March 2020 | Revised: 9 July 2020 | Accepted: 5 August 2020

DOI: 10.1111/jfbc.13460

FULL ARTICLE

Journal of Food Biochemistry WILEY

Noni (*Morinda citrifolia* L.) wine prevents the oxidative stress and obesity in mice induced by high-fat diet

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Abstract

Noni (*Morinda citrifolia L.*) is rich in polyphenols, flavonoids, terpenoids, and iridoids. However, its bad taste and smell make noni fruit unsuitable for consumption. After fermentation, noni wine becomes free from the undesirable smell. Nevertheless, it is still unclear whether processed noni could retain its original nutrients and effects. Therefore, we conducted a series of evaluations on the nutritional composition and efficacy of noni wine. Our results showed that the polyphenol, flavonoid, and vitamin C contents in noni wine were 558.80, 234.42, and 0.30 mg/L, respectively. Our animal experiments showed that 40 ml kg^{-1} day^{-1} noni wine could reduce bodyweight, as well as the levels of body fat, serum triglycerides, total cholesterol, and low-density lipoprotein, while it simultaneously increased the amount of energy expenditure and activity, and improved the systemic antioxidant capacity in mice following a high-fat diet. The results of the gene expression and western blot analyses showed that 40 ml kg^{-1} day^{-1} noni wine could regulate the Nrf2 pathway and improve the antioxidant enzyme gene expression in mice maintained on a high-fat diet, thereby improving body lipid metabolism, reducing fatty acid synthesis, and promoting fatty acid β-oxidation. Our study indicated that drinking 40 ml kg^{-1} day^{-1} noni wine could effectively prevent high-fat diet-induced oxidative stress and obesity in mice.

Practical applications

Noni fruit is rich in nutrients but its bad smell and hardship of processing make its commercialization difficult. Previous studies mainly focused on fresh noni juice and its primary processed products, while few noni products, of poor taste and low quality, are available in the market. Therefore, the fruit wine with both the nutritive values and the special flavor of noni has broad market prospects. Our work provides a valuable reference for the commercialization of noni wine.

KEYWORDS

antioxidant, high-fat diet, lipid metabolism, mice, noni wine, nutrients

1 | INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a common chronic disease worldwide (Targher, Day, & Bonora, 2010) with an estimated global prevalence of approximately 25.24% (Younossi et al., 2016). The NAFLD pathogenesis is not fully understood and involves several factors, such as high-fat diet (HFD), oxidative stress, alterations of lipid metabolism, and insulin resistance (Rolo, Teodoro,

& Palmeira, 2012). Nowadays, NAFLD treatment and control are still limited, and extensive research has been undertaken in order to develop new treatment approaches for the disease.

Several epidemiological studies have demonstrated the correlation between HFD and NAFLD. The long-term consumption of high-fat foods increases the levels of total cholesterol (TC), triglycerides (TG), and free fatty acids in the liver and blood, affecting liver metabolism and reducing the antioxidant activity of such liver enzymes as glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), and catalase (CAT), thereby accelerating the generation of reactive oxygen species (ROS) (Campion, Milagro, Fernandez-Orth, & Alfredo, 2006; Milagro, Campion, & Alfredo, 2006). When the amount of the produced ROS exceeds the scavenging ability, excessive ROS could induce oxidative stress, liver damage, and affect lipid metabolism-related tissues, resulting in decreased lipid metabolism (Wanagat, Dai, & Rabinovitch, 2010). Therefore, maintaining the redox homeostasis would be important in the inhibition of NAFLD.

Noni (*Morinda citrifolia L.*) from the family *Rubiaceae* (coffee family) has been used as a medicinal plant for treating a variety of ailments by Polynesians for over 2000 years. At present, nearly 200 plant chemicals have been identified and isolated from different parts of the noni plant, including organic acids, polysaccharides, plant polyphenols, flavonoids, terpenoids, and iridoids (Bui, Bacic, & Pettolino, 2006). Noni allegedly exhibits antioxidant, hypolipidemic, immune-enhancing, and hepatoprotective effects (Sousa et al., 2018; Zhang, Li, Xia, & Lin, 2013). Polyphenols, flavonoids, and anthraquinones are the main secondary metabolites and bioactive components of the noni fruit (Motshakeri & Ghazali, 2015). Neolignan, americanin A, 3,3′-bisdemethyl-pinoresinol, morindolin, and isoprincepin are reportedly effective antioxidant noni fruit compounds through copper-induced oxidation of low-density lipoprotein test (Kamiya, Tanaka, Endang, Umar, & Satake, 2004). Recently published studies showed that noni fruit polysaccharide could modulate gut microflora and short-chain fatty acids production, reducing colonic barrier permeability and metabolic endotoxemia, thereby reduced hepatic oxidative stress and inflammation in HFD rats (Yang et al., 2020). Despite its numerous beneficial effects, fresh noni fruit cannot be eaten directly due to its bitter taste and unpleasant odor caused by volatile short-chain fatty acids. Moreover, the fresh fruit cannot be stored for a long time (Potterat & Hamburger, 2007). Previous studies mainly focused on fresh noni juice and its primary processed products, while few noni products, of poor taste and low quality, are available in the market (Basar Maurer & Westendorf, 2011). Therefore, the fruit wine with both the nutritive values and the special flavor of noni has broad market prospects.

Noni wine is a low-alcoholic fruit wine made from fermented noni fruits. After fermentation, noni fruit wine could be devoid of the original unpleasant smell of the fruit. Epidemiological studies have shown that moderate low-alcoholic wine consumption (1–2 glasses per day) is associated with health benefits, such as decreased incidence of cardiovascular disease or hypertension (Gepner et al., 2015). These beneficial effects have been attributed to the phenolic compounds in wine increased antioxidant capacity and lipid metabolism (Krenz & Korthuis, 2012). However, it is still unclear whether noni wine could retain the original effects of the noni fruit. Therefore, this study aimed at evaluating how noni wine could affect HFD-induced oxidative stress and lipid metabolism disorder in mice.

2 | MATERIALS AND METHODS

2.1 | Wine analysis

2.1.1 | Noni wine

Noni wine, which is a fruit wine made from fermented noni fruit with an alcohol content of 11% vol. was procured from Zhuzhou Qianjin Pharmacy Co., Ltd. In this study, three bottles were randomly selected from different batches, and repeated experiments were conducted in triplicate.

2.1.2 | Total phenolic content determination

The total phenolic content of the noni wine was determined using the Folin–Ciocalteu reagent following the method of Neergheen et al. after modifications (Neergheen-Bhujun, Soobrattee, Bahorun, & Aruoma, 2006). Different dilution gradients of gallic acid standard solution and noni wine were added to a 10 ml graduated colorimetric tube, then the solutions were supplemented with 2 ml of 15% Na_2CO_3 solution and 1 ml of 0.2 mol/L FC reagent. Finally, the solution was diluted to 10 ml with distilled water. The absorbance was measured at 760 nm after 1 hr incubation in the dark. The results are expressed in milligrams of gallic acid equivalent.

2.1.3 | Total flavonoid content determination

We used the spectrophotometric assay of Zhishen, Mengcheng, and Jianming (1999) after modification in order to assess the total flavonoid content of the noni wine. Rutin standard solution with different dilution gradients was added to a 10 ml graduated colorimetric tube and diluted to 5 ml with a 30% ethanol solution. Next, 0.3 ml of 5% $NaNO_2$ was added to the solution and mixed. In addition, 0.3 ml 10% aluminum nitrate solution was mixed by inversion and incubated for 60 min. Then, 2 ml of 1.0 mol/L NaOH solution and 30% ethanol were mixed with the aluminum nitrate solution and used as a blank control. The absorbance was measured at 510 nm using a spectrophotometer. The results are expressed in milligrams of rutin equivalent.

2.1.4 | Vitamin C content determination

The vitamin C content was determined by titration using 2,6-dichloroindophenol (West, Deng, & Jensen, 2011). The sample was diluted

with a metaphosphoric acid–acetic acid solution (0.03%:0.08%) and mixed for 10 s. Then, the solution was titrated using a 2,6-dichloroindophenol solution until it turned pink for 10 s. Different concentrations of ascorbic acid standard solutions were titrated similarly and under the same conditions as a reference, then the ascorbic acid content of the noni wine was calculated.

2.1.5 | Mineral content determination in noni nine

We subjected 2 ml of the samples to hot digestion, mixing them with 2 ml of 30% H_2O_2 and 1 ml of 65% HNO_3, then heating to a temperature of 75 ℃ until the samples lost their color. The samples were then analyzed using an AA-240 Atomic Absorption Spectrometer equipped with a flame atomizer (F-AAS), graphite furnace (GF-AAS), produced by the Varian Medical Systems (Palo Alto, CA, USA). The analytic method was adapted from a previous study (Boschetti et al., 2013).

2.1.6 | Individual organic acid content determination

The individual organic acid contents were determined based on a previously described method (Frayne, 1986) using an Agilent 1100 instrument (Agilent, CA, USA). A standard quantity (50 mg) of malic, acetic, succinic, formic, butyric, lactic, citric, propionic, and fumaric acids was diluted in 10 ml of 2% ammonium dihydrogen phosphate to obtain the standard solutions. The mixed standard solutions were diluted to 1, 5, 10, 50, 100, 200, and 400 mg per 100 ml of solutions and passed through a 0.45 μm filter. Column: Agilent SB—C_{18} (4.6 mm × 150 mm, 5 μm), Temperature: 30°C, using 0.5% $(NH_4)_2HPO_4$ – H_3PO_4 (pH = 2.0) as the mobile phase at a flow of 1.0 ml/minute. The detection was performed at 210 nm using a detector.

2.2 | Animals and treatments

The study was conducted after obtaining approval from the Institutional Animal Ethics Committee. The 5-week-old male C57BL/6J mice (12.09 ± 0.27 g), that were used in this study, were obtained from the Shanghai Slac Laboratory Animal Co. Ltd. The animal experiment batch number was No. 20170217-20170601 [22]. The mice were housed in individually ventilated cages, where five mice were placed in each cage in a controlled environment (23 ± 2 ℃) with 12-hr light/dark cycles and provided with standard chow and water. After acclimatizing to these conditions, 50 C57BL/6J mice were randomly divided into five groups and their weights were recorded once a week. Mice were received different diet and different doses of noni wine for 13 weeks. The feeding and treatment schedules were as follows:

Group 1 (LFD): low-fat diet (8.9% energy from fat), oral 20 ml/kg body weight (bd. wt.) normal saline;

Group 2 (HFD): high-fat diet (45% energy from fat), oral 20 ml/kg bd. wt. normal saline;

Group 3 (HFD + LN): HFD supplemented with 10 ml/kg bd. wt. noni wine, being equivalent to drinking 75 ml of noni wine per day for an adult human weighing 60 kg;

Group 4 (HFD + MN): HFD supplemented with 20 ml/kg bd. wt. noni wine, being equivalent to drinking 150 ml of noni wine per day for an adult human weighing 60 kg;

Group 5 (HFD + HN): HFD supplemented with 40 ml/kg bd. wt. noni wine, being equivalent to drinking 300 ml of noni wine per day for an adult human weighing 60 kg.

The treatment was delivered daily through oral gavage. The National Institute of Alcohol Abuse and Alcoholism defines "moderate alcohol consumption" to be less than two drinks (28 g) per day for men (McHenry, Alghamdi, & Lisker-Melman, 2018). Therefore, it is safe for adults to drink 300 ml of noni wine on a daily basis, consuming an equivalent of 26 g of alcohol. The mouse alcohol intake simulated the FDA guidance for the industry and reviewers: estimating the safe starting dose in clinical trials for therapeutics in adult healthy volunteers. The conversion was based on the body surface area.

The food intake was calculated based on the average consumption of five mice per cage. The fecal samples were collected by Metabolic PhenoCages (TSE systems, Germany). After 13 weeks of feeding, mice were anesthetized by intraperitoneal injection of pentobarbital 50 mg/kg bd. wt. and sacrificed after heart puncture. The blood samples were centrifuged at 2,000 ×*g* for 10 min, and the clean serum was stored at −80°C for further analyses. The liver, adipose tissue, and gastrocnemius muscle tissue samples were obtained from the sacrificed mice and the organ index was calculated after weighing (Organ weight index = organ weight/body weight × 100%).

2.3 | Fecal fat content measurement

The fecal lipid content was determined as previously described (Jambocus et al., 2017). Briefly, fecal samples (1 g) were soaked in 2 ml of deionized water for 24 hr and homogenized by high-speed vortexing for 60 s. The lipid was extracted using a 7.5 ml of solution of methanol: chloroform (2:1, v:v) and shaken for 30 min. Then 2.5 ml of deionized water and 2.5 ml of chloroform were added to the mixture, which was then shaken for another 30 min. The mixture was then centrifuged at 2,000 ×*g* for 15 min. The lipid layer was collected and dried under vacuum, then the total fat content was weighed.

2.4 | Indirect calorimetric analysis

After 11 weeks, the three groups with the most significant bodyweight differences (LFD, HFD, and HFD + HN) were selected for whole-body metabolic status analysis (four mice per group) by indirect calorimetry using a Comprehensive Laboratory Animal

TABLE 1 Sequence of primers in quantitative real-time reverse transcription polymerase chain reaction

Gene	Forward primer (5′-3′)	Reverse primer (5′-3′)
β-Actin	GGCTGTATTCCCCTCCATCG	CCAGTTGGTAACAATGCCATGT
Gsk-3β	TGGCAGCAAGGTAACCACAG	CGGTTCTTAAATCGCTTGTCCTG
Nrf2	GCCGCTTAGAGGCTCATCTC	TGGGCGGCGACTTTATTCTT
Fas	GCTGGCTCACAGTTAAGAGTTC	GTACTCCTTCCCTTCTGTGCAT
HO-1	GGAAATCATCCCTTGCACGC	TGTTTGAACTTGGTGGGGCT
Srebp1c	GCAGCCACCATCTAGCCTG	CAGCAGTGAGTCTGCCTTGAT
Cyp7a1	GGGATTGCTGTGGTAGTGAGC	GGTATGGAATCAACCCGTTGTC
Pparα	AGAGCCCCATCTGTCCTCTC	ACTGGTAGTCTGCAAAACCAAA
NQO-1	AGGATGGGAGGTACTCGAATC	AGGCGTCCTTCCTTATATGCTA
Acc	GATGAACCATCTCCGTTGGC	GACCCAATTATGAATCGGGAGTG
Cpt-1	CTCCGCCTGAGCCATGAAG	CACCAGTGATGATGCCATTCT

Monitoring System (CLAMS, Columbus Instruments, Columbus, OH) for 24 after 48 hr of habituation following manufacturer's instructions. Lighting and feeding conditions were kept the same as in the home cages (Sun et al., 2015). The oxygen consumption, carbon dioxide production, respiratory exchange ratio (RER = VCO_2/VO_2), energy expenditure (EE = $(3.815 + 1.232 \times RER) \times VO_2$), and ambulatory activity (the total number of occasions per hour when the beam was blocked by mice) were evaluated.

2.5 | Serum and liver lipid assays

Serum and liver TC, TG, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) contents were examined using the corresponding commercial enzymatic colorimetric assay kits (Nanjing Jiancheng Bioengineering Institute, Nanjing, Jiangsu, China) according to the manufacturer's instructions.

2.6 | Tissue homogenate preparation

We homogenized 0.1 g of the liver samples in 0.9 ml of saline solution using a CK1000 high-throughput tissue grinder (Thmorgan, Beijing, China), the supernatants were collected by centrifugation at 3,000 ×*g* for 10 min, then the supernatants were stored at −80°C for further analysis. The protein content in the supernatant was measured using a commercial Enhanced BCA Protein Assay Kit (Beyotime Biotech, Shanghai, China) according to the manufacturer's instructions.

2.7 | Tissue and serum redox homeostasis

ROS, total antioxidant capacity (T-AOC), malondialdehyde (MDA), glutathione (GSH), oxidized glutathione (GSSG), as well as SOD, CAT, and glutathione peroxidase (GSH-Px) activities were tested as tissue and serum antioxidant capacity indices (Chang et al., 2013).

The ROS was determined using a luminol-dependent chemiluminescence assay in the presence of luminal (0.5 mmol/L) and horseradish peroxidase (12 U/mL) (Sigma) using a thermostatically (37°C) controlled luminometer (Xi'an Remex Analysis Instrument, Xi'an, China). The ROS contents are expressed as relative light units (Kobayashi et al., 2001).

The tissue and serum T-AOC, MDA, SOD, CAT, and GSH-Px contents were determined using the corresponding commercial kits obtained from the Nanjing Jiancheng Bioengineering Institute (Nanjing, Jiangsu, China) according to the manufacturer's instructions.

The GSH and GSSG ratios were determined as previously described (Hissin & Hilf, 1976) using the OPT color reaction at a fluorescence excitation and emission wavelengths of 350 and 430 nm, respectively.

2.8 | RNA extraction and quantitative real-time PCR

Total RNA was extracted from the liver and the epididymal adipose tissues using the TRIzol reagent (Sangon Biotech, Shanghai, China) according to the manufacturer's instructions. Following the extraction, the total RNA samples (1,000 ng/μL; 260:280 = 1.8–2.0) were reverse-transcribed to cDNA using a High-Capacity cDNA Reverse Transcription Kit with RNase Inhibitor (Thermo Fisher Scientific, MA, USA). Then real-time PCR was used to determine the relative mRNA expression levels of the target genes. The reaction mixes of 10 μL comprised 10-fold dilutions of cDNA (0.5 μL), 10 μmol/L forward and reverse primers (0.4 μL each), 2 × SYBR Green Master Mix (5.4 μL), and DEPC water (3.7 μL). The PCR cycles consisted of the following steps 95°C for 5 min; then 40 cycles of 95°C for 20 s; 62°C for 30 s; 72°C for 20 s, and 72°C for 2 min. Using β-actin as an internal reference, the $2^{-\triangle\triangle Ct}$ was used to calculate the relative expression of each group. The transcript abundance was assessed by real-time PCR using the 7,900 real-time PCR system (Applied Biosystems, Foster City, CA, USA) with a SYBR Green detection system. The list of the primers used in this study is summarized in Table 1.

2.9 | Western blot analysis

The western blot analysis was performed as previously described (Yu et al., 2016). The liver samples were homogenized in RIPA buffer including 1 mmol/L phenylmethylsulfonyl fluoride. The mixtures were placed in an ice bath for 30 min before centrifugation (10,000 ×g for 10 min at 4°C). After obtaining the supernatants, the protein contents were quantified using the BCA method, leveled to the same concentration, and were supplemented with 5× loading buffer. The mixtures were placed in a metal bath and heated at 95°C for 15 min. The mixtures were separated using SDS–PAGE, then transferred to cellulose nitrate membrane according to the standard scheme. Next, the nitrocellulose membranes were incubated with the primary antibodies (Abcam, Shanghai, China) at a dilution of. The membrane was then probed with a secondary antibody (Goat vs rabbit IgG, Lincoln, NE, USA). The bands were analyzed using the ImageJ software and the expression ratios were normalized to the expression ratio of β-actin. The catalog numbers of the antibodies used in this study are listed in Table 2.

2.10 | Histopathological analysis

For the histopathological analysis, the liver and the epididymal adipose tissue samples of the suitable size for further sectioning were fixed in formalin. Next, the tissue samples were dehydrated in graded alcohol, cleared in xylene, and embedded in paraffin wax. After processing, the tissues were sectioned into 5-μm-thick slices and stained with Hematoxylin and Eosin (Nanjing Jiancheng Bioengineering Institute, Nanjing, Jiangsu, China). The adipocyte area was calculated using ImageJ software.

2.11 | Statistical analysis

All data are expressed as mean ± *SEM*. The Statistical Package for the Social Sciences software (version 23.0) was used for the data analysis. The *p*-values of less than .05 were considered statistically significant. For the analysis of the differences in the biochemical measures between the five groups, one-way ANOVA (Analysis of Variance) was used. This was followed by Tukey post-hoc test.

TABLE 2 Western blotting antibody molecular weight and catalog number

Antibody	Molecular weight (kDa)	Catalog numbers
β-Actin	43	ab5694
HO-1	30	ab13243
NQO-1	31	ab34173
Nrf2	72	ab92946
Gsk-3β	47	ab131356
PI3K	85	ab19160
Pparα	55	ab24509
Cpt-1	88	ab83862
Srebp-1c	120	ab28481
Acc	280	ab109368
Fas	273	ab22759

3 | RESULTS

3.1 | Noni wine nutrient contents

The results of the component analysis are shown in Table 3. The polyphenol, flavonoid, and vitamin C contents were 558.80, 234.42, and 0.30 mg/L, respectively. The mineral element consisted of mainly Ca, K, Mg, and Na. The organic acid components mainly included lactic, malic, acetic, and citric acids, playing an important role in noni wine production and stability.

3.2 | Effect of noni wine on bodyweight, adipose tissue weight, food intake, and fecal fat content

After 13 weeks of feeding, the HFD group exhibited significantly higher bodyweights and adipose tissue weights than the LFD group. In addition, the HFD + LN and HFD + MN groups exhibited significantly higher bodyweights than the LFD group, while the HFD + HN group exhibited significantly lower body and adipose tissue weights than the HFD group, which showed the same results as the LFD group (Figure 1b and c). The energy intake of the four HFD-fed

TABLE 3 Chemical composition of noni wine

Assay (mg/L)	Mean	*SD*
Total phenolic	558.80	0.71
Total flavonoid	234.42	4.28
Vitamin C	0.30	0.003
Ca	80.10	13.45
K	78.21	0.32
Mg	45.75	8.94
Na	34.04	7.04
Zn	1.60	0.76
Fe	1.13	0.38
Cu	0.11	0.01
Lactic acid	157.24	6.34
Malic acid	144.10	7.25
Acetic acid	143.45	4.62
Citric acid	142.57	2.30
Formic acid	74.40	7.73
Propionic acid	66.89	1.94
Succinic acid	51.85	0.98
Butyric acid	5.66	0.30
Fumaric acid	0.19	0.02

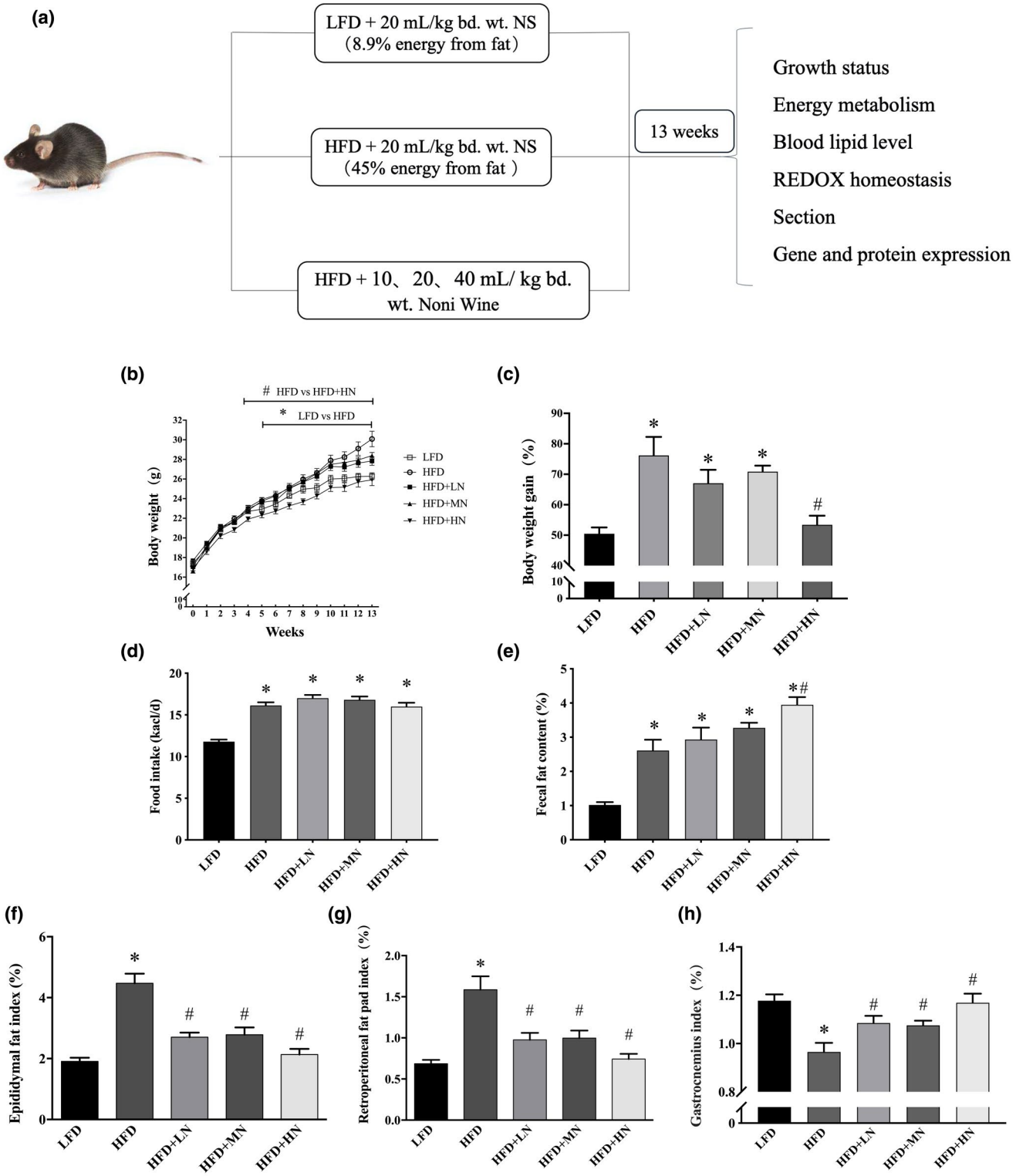

FIGURE 1 Effect of noni wine on body weight and weight gain, organ weight index, food intake and fecal fat content. (a) Experimental scheme; (b, c) Body weight and body weight gain; (d, e) Food intake and fecal fat content; (f, g, h) Organ weight index. HFD, group fed a high-fat diet; HN, group supplemented with 40 mL/kg bd. wt. noni wine; LFD, group fed a low-fat diet; LN, group supplemented with 10 mL/kg bd. wt. noni wine; MN, group supplemented with 20 mL/kg bd. wt. noni wine. Values indicate the mean ± SEM of $n = 10$ mice per group. * indicates significant difference from the LFD group ($p < .05$). # indicates significant difference from the HFD group ($p < .05$)

groups was significantly higher than that of the LFD group. However, the different doses of noni wine intake did not significantly affect the energy intake in mice (Figure 1d). In addition, the HFD significantly increased the fecal fat content in mice. The fecal fat content in the HFD + HN group was significantly higher than that in the HFD group but showed no significant difference between the medium- and low-dose groups and the HFD group (Figure 1e). These results indicated that appetite suppression might not be the main involved anti-obesity mechanism. As the mice organ index indicates, the organ fat level significantly increased, while the gastrocnemius muscle index decreased in the HFD group. After the supplementation of different noni doses, the organ fat level was significantly lower than that in the HFD group and the gastrocnemius muscle index was significantly higher than that in the HFD group, especially in the high-dose group (Figure 1f–h).

3.3 | Serum parameters

As highlighted in Table 4, the blood lipid analysis in mice showed that after 13 weeks, the TG, TC, and LDL levels in the HFD group were significantly higher than those in the LFD group, while we could observe no significant difference in the HDL levels. However, the HFD combined with high-dose noni wine reduced the blood TC, TG, and LDL levels in mice. The medium noni wine dose significantly reduced the TC and LDL levels, and the low-dose noni wine significantly affected only the LDL levels. Compared to the low and medium doses, high-dose noni wine more significantly affected the blood lipid levels in HFD-fed mice.

3.4 | Whole-body metabolic status

The mice of the HFD + HN group gained less weight than the HFD-fed mice. Apart from the differences in fecal fat levels, we hypothesized that noni wine consumption would increase energy expenditure. In order to confirm this idea, we performed 24-hr indirect calorimetric measurements on the LFD, HFD, and HFD + HN groups. As shown in Figure 2, the RER determination over a 24-hr period demonstrated that HFD mice exhibited significantly decreased RER values compared to the LFD mice in the total time ($p < .05$), indicating that HFD induces a metabolic shift toward increased use of lipids as substrates. At the same time, the HFD + HN group showed significantly decreased RER values compared to the HFD group during the night cycle ($p < .05$), suggesting that noni wine might play a significant role in fat metabolism. We observed no difference in the oxygen consumption between the HFD and LFD groups, while the HFD + HN group exhibited significantly higher oxygen consumption levels than the LFD and HFD groups ($p < .05$). During the entire experiment, the energy consumption in the HFD group was higher than that in the LFD group. Compared to the HFD group, the energy consumption of mice ingesting high-dose noni wine significantly increased ($p < .05$). The mice in the HFD group exhibited significantly lower activity at night than those in the LFD group, while the mice in the HFD + HN group exhibited significantly higher daytime activity than those in the HFD group ($p < .05$), suggesting that autonomic activity might play a role in controlling bodyweight.

3.5 | Effect of noni wine on the redox steady-state

Due to the low lipid accumulation in HFD-fed and noni wine-ingesting mice, we hypothesized that the hepatic lipid peroxidation and oxidative damage in the HFD-fed mice are alleviated by noni wine supplementation. As shown in Table 5, the serum and liver ROS and MDA levels of the HFD group were significantly higher than those of the LFD group ($p < .05$). Moreover, the serum GSH-Px and SOD levels, as well as the liver CAT levels decreased, indicating that a HFD could induce oxidative stress in obese mice. Compared to the HFD group, the ROS levels significantly decreased in the HFD + MN and HFD + HN groups, whereas the serum T-AOC levels significantly increased ($p < .05$). The high-dose noni wine also decreased liver ROS and MDA levels ($p < .05$). Meanwhile, high-dose noni wine significantly increased both the serum and liver antioxidant enzymatic activities ($p < .05$).

As shown in Figure 3a, the Gsk-3β gene expression in the HFD group was significantly upregulated compared to that in the LFD group, and the gene expression levels of Nrf2 were downregulated. Compared to the HFD group, high-dose noni wine supplementation significantly lowered the Gsk-3β expression, while it significantly increased the PI3K, Nrf2, NQO-1, and HO-1 expression levels. Compared to the LFD group, we could also observe significantly

TABLE 4 Effect of noni wine on plasma lipid status

Group	TC (mmol/L)	TG (mmol/L)	HDL (mmol/L)	LDL (mmol/dL)
LFD	1.43 ± 0.11	1.73 ± 0.08	0.43 ± 0.07	0.57 ± 0.06
HFD	1.73 ± 0.16*	2.72 ± 0.07*	0.39 ± 0.24	0.72 ± 0.09*
HFD + LN	1.66 ± 0.10	2.79 ± 0.11*	0.38 ± 0.17	0.63 ± 0.04#
HFD + MN	1.12 ± 0.10#	2.72 ± 0.15*	0.45 ± 0.16	0.58 ± 0.10#
HFD + HN	1.23 ± 0.15#	2.34 ± 0.05*	0.58 ± 0.08*	0.42 ± 0.12#

Values indicate the mean ± *SEM* of $n = 10$ mice per group.

*Mean value was different from that of the LFD group ($p < .05$);

#Mean value was different from that of the HFD group ($p < .05$).

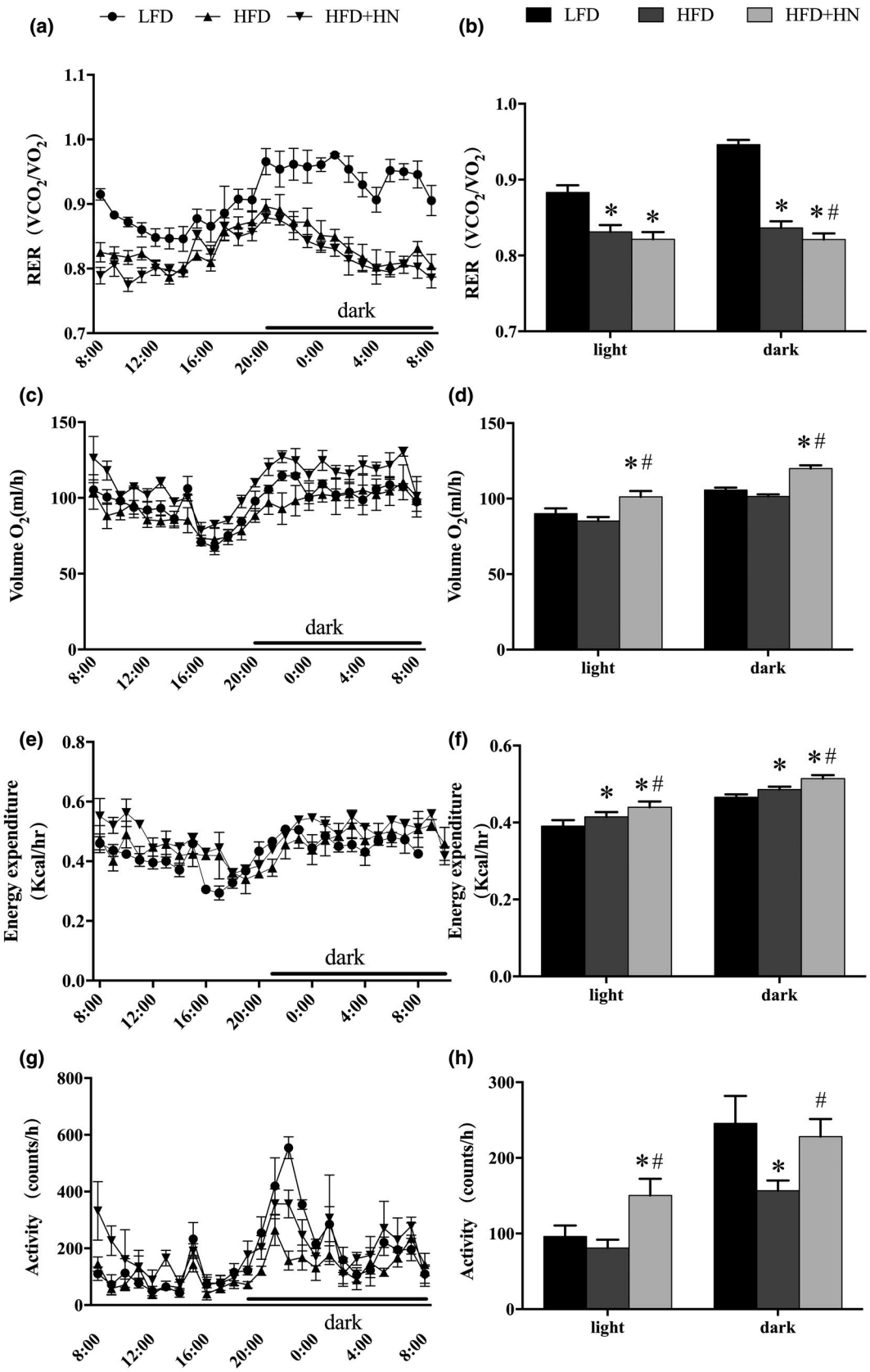

FIGURE 2 Effect of noni wine on whole body metabolic status. (a and b) respiratory exchange ratio (RER); (c and d) volume of oxygen consumption; (e and f) energy expenditure; (g and h) activity. Bar graphs represent cumulative values during the light and dark cycles. Values indicate the mean ± SEM of $n = 4$ mice per group. *Mean value was different from that of the LFD group ($p < .05$). #Mean value was different from that of the HFD group ($p < .05$)

TABLE 5 Oxidative stress biomarkers in liver and serum of mice

Group	ROS (10^3cd/mL)	T-AOC (U/mg)	MDA (nmol/mg)	GSH/GSSG	GSH-Px (U/mg)	SOD (U/mg)	CAT (U/mg)
Serum							
LFD	17.66 ± 3.47	6.24 ± 0.31	2.30 ± 0.14	3.79 ± 0.28	760.00 ± 43.58	79.48 ± 9.69	3.97 ± 0.52
HFD	23.68 ± 4.55*	5.53 ± 0.19*	2.98 ± 0.27*	3.44 ± 0.14	672.00 ± 44.12*	60.91 ± 3.39*	3.30 ± 0.35
HFD + LN	19.64 ± 6.54	6.71 ± 0.30	2.93 ± 0.39	4.34 ± 0.05	671.00 ± 47.57*	75.50 ± 7.50	3.34 ± 0.32
HFD + MN	11.42 ± 2.52#	7.12 ± 0.34*	3.03 ± 0.27	4.17 ± 0.09	644.89 ± 36.08*	78.94 ± 8.01	3.23 ± 0.32
HFD + HN	11.73 ± 3.93#	7.77 ± 0.38*	2.33 ± 0.43#	4.16 ± 0.34	705.33 ± 31.44	102.29 ± 8.54*	4.22 ± 0.68
Liver							
LFD	26.40 ± 4.96	1.05 ± 0.08	3.93 ± 0.18	2.45 ± 0.15	776.02 ± 79.82	58.94 ± 3.99	19.64 ± 1.68
HFD	50.57 ± 6.05*	0.78 ± 0.07*	4.68 ± 0.16*	2.44 ± 0.15	753.14 ± 59.64	50.76 ± 3.47	14.16 ± 1.61*
HFD + LN	63.43 ± 12.94*	0.97 ± 0.11	3.81 ± 0.46	2.43 ± 0.13	947.10 ± 93.98	62.90 ± 5.31	17.18 ± 2.25
HFD + MN	56.35 ± 13.34*	1.20 ± 0.09#	3.91 ± 0.28	2.49 ± 0.13	1,039.06 ± 97.88*	64.40 ± 5.02	17.66 ± 1.32
HFD + HN	32.75 ± 8.82#	1.17 ± 0.14#	3.32 ± 0.32#	2.98 ± 0.08	1,091.84 ± 180.58*	78.73 ± 6.64*	19.91 ± 2.38#

Values indicate the mean ± *SEM* of $n = 10$ mice per group.

*Mean value was different from that of the LFD group ($p < .05$);

#Mean value was different from that of the HFD group ($p < .05$).

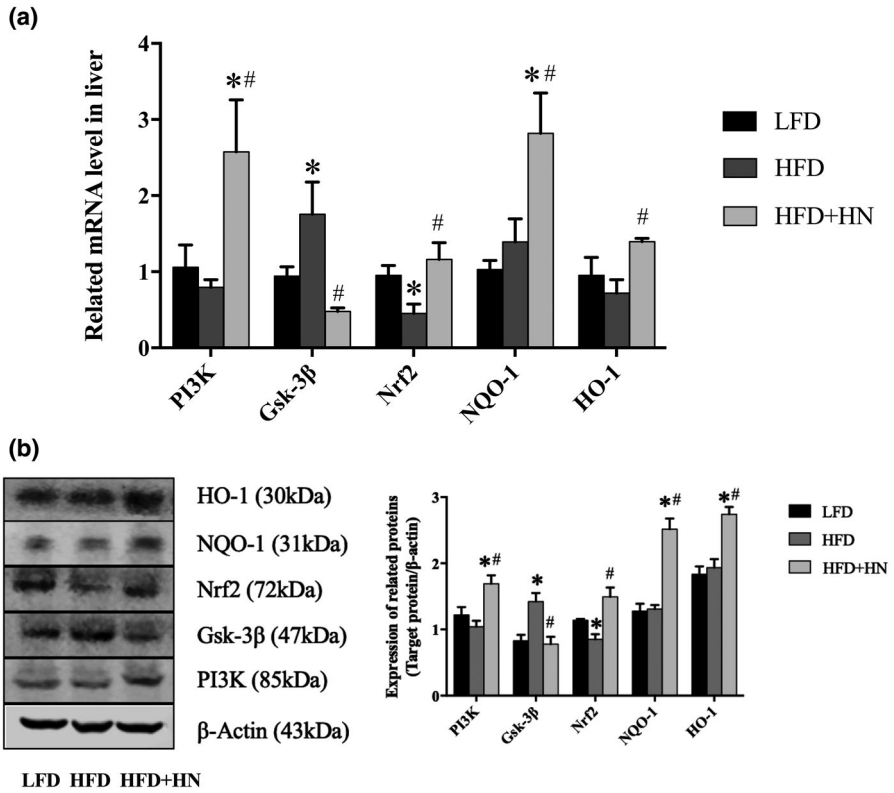

FIGURE 3 Effects of noni wine on the expression of oxidation-related genes. (a) Relative mRNA level in liver; (b) Expression of related proteins in liver. Values indicate the mean ± SEM of $n = 4$ mice per group. *Mean value was different from that of the LFD group ($p < .05$). #Mean value was different from that of the HFD group ($p < .05$)

improved PI3K and NQO-1 expression levels in the liver of the HFD + HN group mice. The liver protein expression showed that HFD increased Gsk-3β expression and decreased Nrf2 expression in mice, while these expression levels were restored to normal level upon high-dose noni wine supplementation, showing no significant differences from the LFD group. The expression levels of PI3K, NQO-1, and HO-1 in the HFD + HN group were significantly upregulated compared to those in the LFD and HFD groups (Figure 3b).

These results indicated that noni wine might potentially influence the antioxidative pathways in mice.

3.6 | Effect of noni wine on lipid metabolism

In order to understand how noni wine could affect lipid metabolism, we investigated the expression of lipid-regulating genes in the liver and adipose tissue. As shown in Figure 4a and b, the expression of SREBP-1C in the liver of the HFD group mice increased compared to that in the liver of the LFD group mice, while the expression of Cyp7a1 and PPARα decreased significantly ($p < .05$). The expression levels of ACC and SREBP-1C in the adipose tissue also increased significantly ($p < .05$). This indicated that HFD results in increased fat synthesis, decreased lipid metabolism, and ultimately, weight gain. Compared to the HFD group, the expression levels of Fas, ACC, and SREBP-1C in the HFD + HN group decreased, while the CPT-1 and Cyp7a1 expression levels significantly increased in the liver ($p < .05$). The Fas and SREBP-1C expression levels significantly decreased, while the CPT-1 and PPARα expression levels significantly increased ($p < .05$) in the adipose tissue of the HFD + HN group mice. In addition, the ACC expression in the liver of the HFD + HN group mice was significantly lower than that of the LFD group mice, and the CPT-1 and PPARα expression levels in the adipose tissue were significantly higher ($p < .05$). The results of the western blot analysis showed that, compared to the LFD group, the expression levels of Fas, ACC, and SREBP-1C were significantly upregulated in the HFD group. The expression levels of Fas, ACC, and SREBP-1C in the HFD + HN group significantly decreased, and the expression levels of CPT-1 and PPARα significantly increased ($p < .05$) compared with the HFD group (Figure 4c). These results indicate that high-dose noni wine could reduce the level of body fat synthesis and promote fatty acid β-oxidation.

These results were consistent with the histological analysis of liver and adipose tissue in the. HFD increased the level of microvesicular steatosis (arrows) around the central vein and the blurred

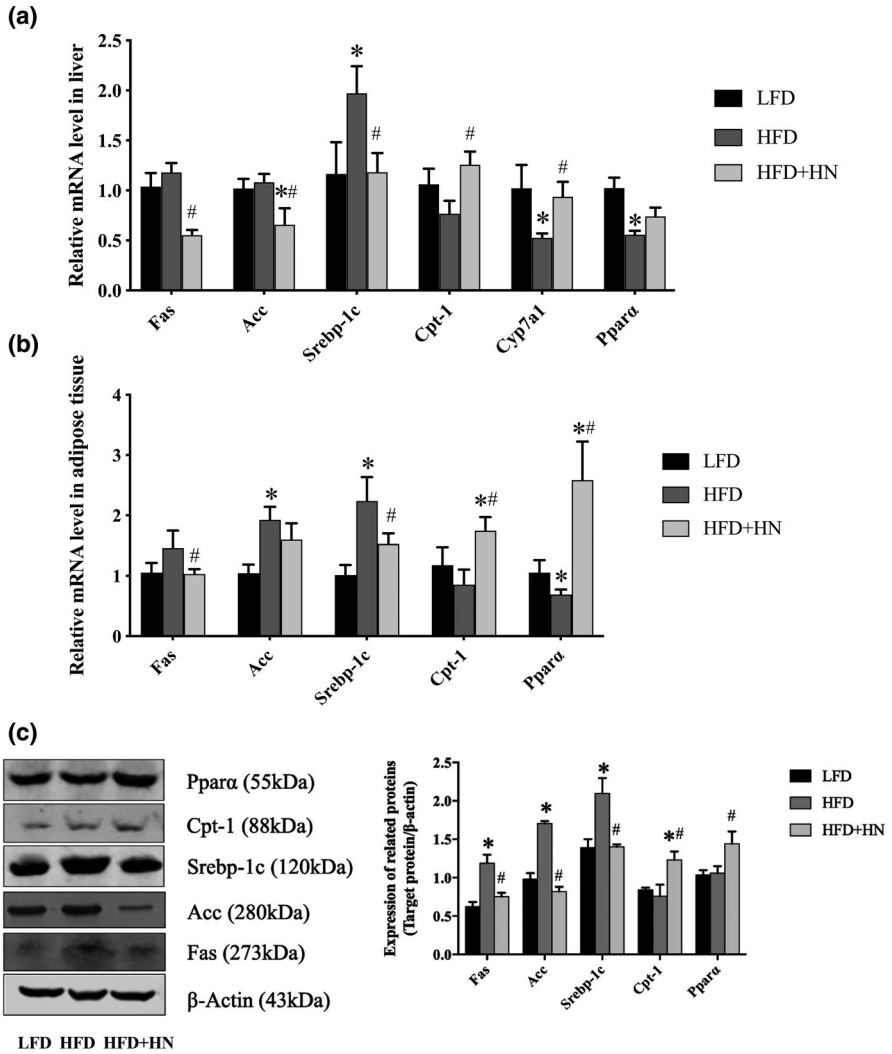

FIGURE 4 Effects of noni wine on mRNA expression of lipid metabolism. (a) Relative mRNA level in liver; (b) Relative mRNA level in adipose tissue; (c) Expression of related proteins in liver. Values indicate the mean ± SEM of $n = 4$ mice per group. *Mean value was different from that of the LFD group ($p < .05$). #Mean value was different from that of the HFD group ($p < .05$)

cellular boundaries, while high-dose noni wine supplementation reduced these (Figure 5a). The liver TG and TC levels significantly increased in the HFD group and were restored to normal levels upon high-dose noni wine supplementation (Figure 5b and c). The stained adipocytes in the epididymal white adipose tissues of the HFD-fed mice were significantly larger than those of the LFD and HFD + HN group mice (Figure 5d).

4 | DISCUSSION

Over the past decade, numerous pieces of evidence have been gathered, supporting the hypothesis that ROS mediate oxidation processes, and their specific products are central to the development of NAFLD and obesity (Roberts & Sindhu, 2009). Several epidemiological studies suggest that red wine consumption might contribute to free radical scavenging (an important indicator of antioxidant capacity) due to the contained antioxidants and reduce the risk of cardiovascular disease (Bede et al., 2020). These effects of red wine have been attributed to its polyphenol content (Chen, Wang, Ma, & Zhai, 2012). In this study, we demonstrated that noni wine prevents HFD-induced lipid metabolism disorder. The possible underlying mechanisms could be explained through the effect by which noni wine improved the HFD-induced oxidative stress and reduced fat absorption.

Reactive oxygen species are a series of highly oxidizing substances produced in the human body during oxygen metabolism, including superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and superoxide anion (OH). These are the three main free radicals with extremely high oxidation activity and the risk of attacking macromolecular substances in the human body, thus leading to protein oxidation, RNA lysis, lipid peroxidation, etc. (Valko et al., 2007). ROS generation and elimination would generally remain at a relatively balanced and stable state, due to the activity of non-enzymatic (vitamin C, GSH, etc.) and enzymatic antioxidants (SOD, CAT, GSH-Px, etc.). However, when the amount of the generated ROS exceeds the systemic scavenging capacity, it would lead to oxidative stress. In such cases, excessive ROS would attack the lipid metabolism-related

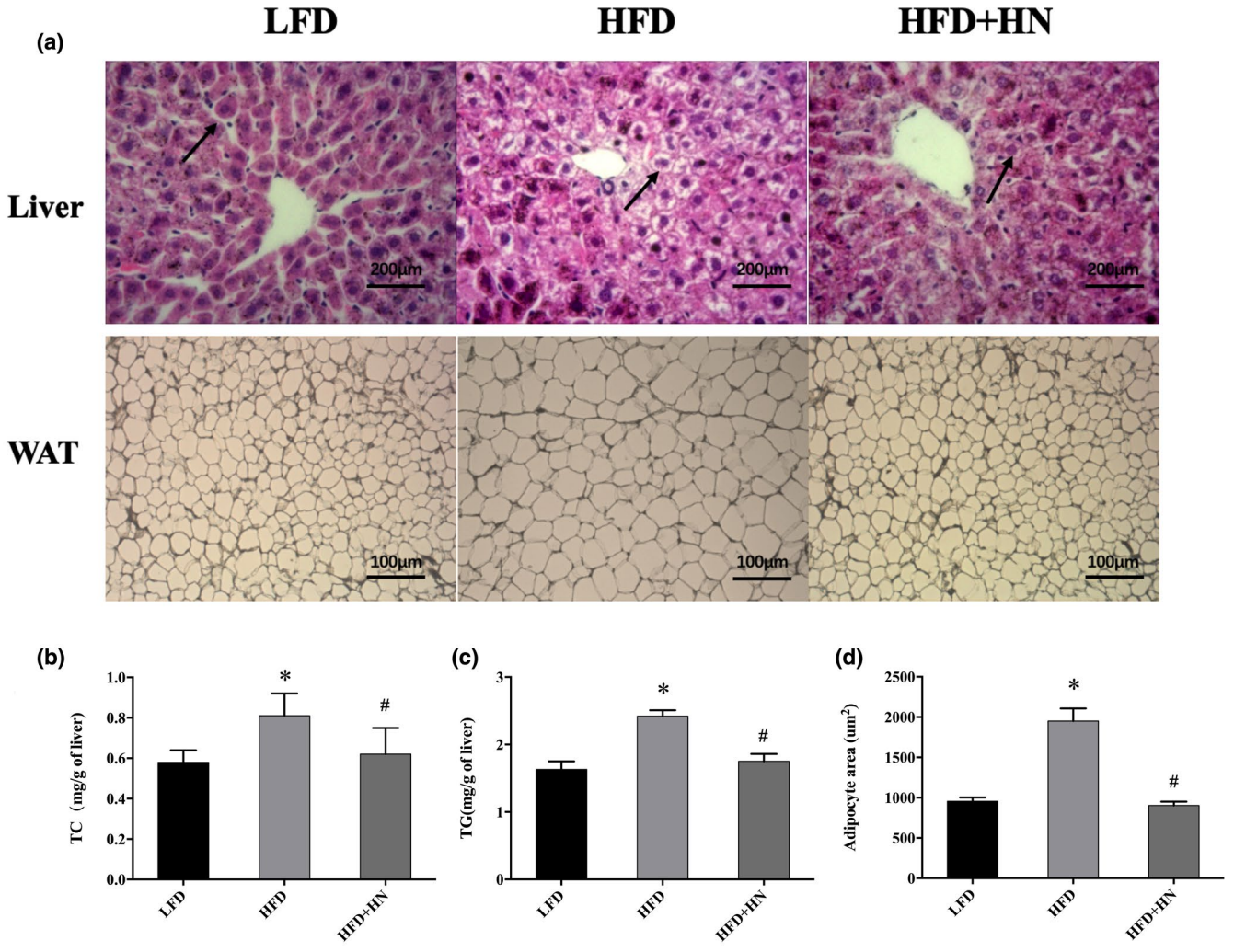

FIGURE 5 Histological analysis. (a) H&E stain under microscope of liver and fat in the experimental mice; (b) Triglyceride content in liver; (c) Total cholesterol in the liver; (d) Adipocyte area. Values indicate the mean ± SEM of $n = 10$ mice per group. *Mean value was different from that of the LFD group ($p < .05$). #Mean value was different from that of the HFD group ($p < .05$)

tissues, resulting in lipid metabolism disorder (Wanagat et al., 2010). Therefore, maintaining the redox homeostasis at a balance is an important way to inhibit NAFLD.

The content of polyphenols, flavonoids, and vitamin C in noni wine was 558.80 mg/L, 234.42 mg/L, and 0.30 mg/L, respectively. Mineral elements were mainly Ca, K, Mg, and Na. The organic acids were mainly lactic acid, malic acid, acetic acid, and citric acid. Rich phytochemicals, such as polyphenols, flavonoids, and tannins grant noni wine a strong antioxidant effect (Sobhani, Farzaei, Kiani, & Khodarahmi, 2020). In this study, noni wine was supplemented to HFD-fed C57BL/6J mice, resulting in the improved expression of both antioxidant- and lipid metabolism-related genes. Therefore, we could conclude that noni wine could be used as a potential therapeutic agent against HFD-induced oxidative stress.

HFD-induced oxidative stress could damage the body both directly and indirectly. However, the body has developed an oxidative stress response system to efficiently defend itself against such damages. The Gsk-3β/Nrf2 signaling pathway, as an important cellular antioxidant pathway, plays a significant role in regulating the redox state of the body (Buendia et al., 2016). In this study, we investigated the expression levels of key genes in the Gsk-3β/Nrf2 signaling pathway in order to determine the effector mechanisms, by which noni wine could increase the antioxidant capacity in mice. The results showed that high-dose noni wine could significantly increase the PI3K and Nrf2 expression while inhibiting the Gsk-3β expression, thus increasing the expression of downstream antioxidant enzyme-related genes. Previous studies have shown that moderate red wine intake decreased pro-inflammatory factors and increased total antioxidant capacity despite a fat-enriched diet intake in healthy young volunteers, which is consistent with our research (Torres et al., 2015). The apparent indexes indicated that high-dose noni wine supplementation could significantly improve the activities of SOD, CAT, GSH-Px, and other antioxidant enzymes in HFD-fed mice, improving the total antioxidant capacity and reducing the content of MDA, a lipid peroxidation biomarker.

Red wine intake can prevent the increase of liver NF-κB activity caused by high-fat diet, reduce inflammation and malondialdehyde concentration, thereby improving lipid metabolism and lowering blood lipid levels (Lauer Macedo et al., 2013; Romain et al., 2014). In this study, we found that high-dose noni wine supplementation could reduce the HFD-induced bodyweight and body fat in mice, as well as the levels of serum TC, TG, and LDL. Compared with the LFD group, the level of HDL in the HFD + HN group increased but was not significantly different from that of the HFD group. Among several obesity treatment methods, inhibiting nutrient absorption and increasing fat metabolism are promising strategies (Bray & Tartaglia, 2000). Previous studies have shown that phenols could inhibit pancreatic lipase, increase TG excretion in feces, and directly reduce intestinal fat absorption (McDougall, Kulkarni, & Stewart, 2008). Our data indicate that the fat content in the feces of the HFD + HN group is higher than that in the feces of the HFD group. This means that the weight reduction effect of noni wine might be partially related to the increased feces fat content. However, the increased feces fat content is only a small fraction of the intake (about 1–2%). Low-dose noni wine supplementation reduced the adipose tissue index, while the fecal fat content did not increase. Therefore, this mechanism might not be a major factor in the slow weight gain of mice supplemented with high-dose noni wine. Another important reason for fat reduction might be an improvement in fat metabolism in the liver and acceleration of fatty acid β-oxidation (Horton, Goldstein, & Brown, 2002). Therefore, it is necessary to further explore how noni wine could affect metabolism.

The metabolic data indicate that the RER value of HFD-fed mice could be significantly reduced, indicating a metabolic shift toward increased use of lipids as a substrate with significant differences between the HFD and HFD + HN groups. According to previous reports, 90% of the oxygen consumption occurs in the mitochondria, 80% of which is related to ATP synthesis. The body could enhance respiration and energy use by increasing oxygen consumption (Hong et al., 2015). In good agreement with the conclusions of this study, the oxygen consumption in the HFD + HN groups increased significantly, and the daily energy consumption in the HFD + HN group was significantly higher than that in the HFD group. In addition, the activity of HFD-fed mice decreased significantly at night, while the activity of mice in the HFD + HN group increased significantly. This is one of the important reasons why mice in the HFD + HN group gained less weight than those in the HFD group. Increased activity and energy expenditure would inevitably increase fat metabolism (Teske, Billington, Kuskowski, & Kotz, 2011).

Fas is the key enzyme controlling the fatty acid synthesis rate. ACC is the rate-limiting enzyme in long-chain fatty acid biosynthesis and is mainly responsible for regulating fatty acid synthesis (Li et al., 2020). PPARα is a fatty acid receptor and a major transcription factor of the fatty acid oxidase gene, which could maintain physiological-level lipid- and energy metabolism and promote the transfer and use of fatty acids in the liver by regulating lipoprotein metabolism and inhibiting fatty acid and TG synthesis. CPT-1α is the rate-limiting enzyme in fatty acid β-oxidation. CYP7A1 is the rate-limiting enzyme in bile acid synthesis and metabolism (Wang et al., 2020). Our data show that a HFD could increase SREBP-1C expression, while high-dose noni wine supplementation could reduce it, thereby reducing the expression of Fas and ACC and finally reducing fat synthesis. Meanwhile, high-dose noni wine could also increase the expression of CPT-1 and PPARα in the adipose tissue and promote the consumption of fatty acids, which might be an important reason for increased energy consumption in mice. In addition, the consumption of high-dose noni wine could inhibit the synthesis of bile acid and reduce fat absorption to a certain extent.

It is universally acknowledged that heavy drinking could have multiple harmful effects on health (Seitz & Stickel, 2007). However, whether consuming moderate and small amounts of fruit wine could reduce the prevalence of NAFLD is still debatable. Based on this controversy, we conducted this study in order to clarify the advantages and disadvantages of moderate supplementation of noni wine (containing high levels of polyphenols) on liver steatosis using an in vivo fatty liver model. Our results showed that moderate noni wine supplementation was not only safe but also helpful in eliminating liver steatosis in mice.

This study provides significant new pieces of evidence for the noni wine-mediated improvement of HFD-induced oxidative stress and lipid metabolism disorder. The underlying effector mechanisms might be related to the effect of polyphenols on antioxidant enzyme activities in mice, maintaining the redox homeostasis under HFD conditions, and promoting lipid metabolism. However, further contributions from other unknown mechanisms cannot be excluded. As a new fruit wine product, noni wine could possess broad prospects in the international market.

5 | CONCLUSION

The results of this study showed that noni wine is rich in polyphenols, flavonoids, and other nutrients. And 40 ml kg^{-1} day^{-1} of noni wine prevented HFD-induced bodyweight and body fat gain in mice. In addition, noni wine consumption reduced fat absorption, as well as the levels of serum TG, TC, LDL, while it increased oxygen consumption and activity in mice to increase energy expenditure. Our study also indicated that 40 ml kg^{-1} day^{-1} of noni wine intake increased the levels of PI3K, Nrf2, NQO-1, and HO-1 and inhibited the expression of Gsk-3β, reduced systemic ROS and MDA levels, and improved the activity of SOD, CAT, GSH-Px, and other antioxidant enzymes. This resulted in an improved response to HFD-induced oxidative stress. At the same time, noni wine also reduced the expression of Fas, ACC, and SREBP-1C, increased the expression of CPT-1 and PPARα, reduced lipid synthesis, and promoted fatty acid β oxidation in HFD-fed mice.

ACKNOWLEDGMENTS

This study was conducted at Jiangnan University. And authors are grateful to the school of food science and technology for providing an instrument and experimental platform for the experiments during the research period. We were grateful to Qianjin Pharmacy Co., Ltd for providing the noni wine used in this study and thanks to Jun Meng and Xiaojuan Li for providing guidance for our experimental design.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

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How to cite this article: Zhang K, Meng J, Li X, et al. Noni (*Morinda citrifolia* L.) wine prevents the oxidative stress and obesity in mice induced by high-fat diet. *J Food Biochem*. 2020;44:e13460. https://doi.org/10.1111/jfbc.13460