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Extraction of raspberry ketone from red raspberry and its intervention in the non-alcoholic fatty liver disease

Yongqiang Ma*, Weiye Xiu, Xin Wang* and Qiuhui Yang

Abstract

Nonalcoholic fatty liver disease (NAFLD) is characterized by diffused hepatocyte bullous fat in the liver, which is not caused by alcohol or drugs like amiodarone and tamoxifen. Presently, no drug is approved for NAFLD treatment. Therefore, it's important to extract effective components from natural plants to alleviate NAFLD. In this study, we extracted and purified raspberry ketone, a natural phenolic compound from red raspberry (*Rubus ideaus* L.) by an ultrasonic-assisted ethanol extraction method. The structure of red raspberry ketone (RRK) was determined using Fourier-transform infrared spectroscopy and the purity of RRK was found as 80.06 ± 1.19%. After 28 days of intragastric administration of RRK, the bodyweight of NAFLD model rats decreased significantly ($p < 0.05$). Besides, the levels of low-density lipoprotein cholesterol, total cholesterol, and total triglyceride (TG) decreased and the content of high-density lipoprotein cholesterol in serum increased drastically. Moreover, the level of liver damage indicators (aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase) and the levels of glucose, insulin, free-fatty acid, tumor necrotic factor-α in the liver decreased distinctly. The levels of TG and malondialdehyde in the liver decreased, whereas the levels of superoxide dismutase, total glutathione, and glutathione peroxidase drastically increased. We also found that RRK reduced the uneven size of liver cells and blurred boundaries of hepatic lobules, and alleviated hepatic steatosis and inflammation caused by NAFLD. We inferred that RRK could relieve NAFLD progression by regulating glucose and lipid metabolism and alleviating oxidative stress in vivo. This study sheds new light on the use of RRK as a functional food for NAFLD prevention.

Keywords: Red raspberry ketone, Extraction and purification, NAFLD, Functional food

Introduction

Non-alcoholic fatty liver disease (NAFLD) is defined as hepatic steatosis characterized by the absence of other pathogenic factors of liver disease, such as chronic viral hepatitis and the presence of hepatic fat accumulation (> 5%) [1]. The pathogenesis of NAFLD is complex. Metabolic abnormalities caused by excess fat in the liver and the development of inflammation can trigger NAFLD. At present, the "two-hit" theory is a relatively comprehensive explanation of the pathogenesis of NAFLD [2, 3]. The theory states that the first hit is caused by abnormal lipid intake or abnormal mitochondrial function in the body because of obesity or type 2 diabetes, which causes massive lipid accumulation in the hepatocytes. This results in triglyceride deposition in the liver or steatosis, which increases the chance of liver damage mediated by the "second hit" [4]. The "second hit" is caused by oxidative stress and lipid peroxidation in the hepatocytes, which causes mitochondrial dysfunction, production of inflammatory mediators, and activation of hepatic stellate cells, resulting in inflammatory necrosis and fibrosis of the hepatocytes [5]. Recently, some researchers also found the multiple hit theory was also another explanation of

*Correspondence: qyma126@163.com; wangxinfood@163.com

College of Food Engineering, Harbin University of Commerce, Heilongjiang Provincial Key Laboratory of Cereals and Comprehensive Processing of Cereal Resources, Harbin 150028, Heilongjiang, China

the pathogenesis of NAFLD, such hits were associated with insulin resistance and abnormal glucolipid metabolism, which is harmful to our health [6, 7]. NAFLD has a high incidence in developed industrial countries in recent years [8]. NAFLD treatment consists mainly of lifestyle changes and adjunctive medication. However, no definitive drug is available for the NAFLD-treatment [9]. Drugs that are used for the NAFLD-treatment include statins and fibrates, which can alleviate NAFLD by regulating abnormalities in lipid metabolism. However, these drugs have some side effects such as gastrointestinal discomfort and impairment of liver and kidney function [10]. To address this concern, some studies have focused on the effectiveness of the nature bioactive compounds such as Lee et al.'s and Shah et al.'s studies [11, 12]. Moreover, Li et al. also reported that a plant based bioactive compounds, eugenol, had a positive effect on NAFLD via regulate lipid metabolism [13]. Similarly, another study also reported that an extract from cranberry can improve insulin sensitivity to lower blood glucose levels and increase antioxidant and anti-inflammatory activities in vivo [14].

Red raspberry (*Rubus ideaus* L.) is a natural plant that has a distinctive red color and a delicious flavor that is popular among consumers. Red raspberry is recommended worldwide by the Food and Agriculture Organization of the United Nations as one of the key fruits of the third generation, i.e. the fruits distributed in the wild forest area which has not been exploited and some newly developed special fruits. [15]. Previous study has reported that red raspberry is rich in active ingredients, such as ellagic acid and anthocyanin, which has antioxidant, anti-inflammatory, and anti-cancer properties [16]. Red raspberry can also improve glucolipid metabolism [17]. Luo et al. reported that the consumption of red raspberries every day markedly reduces hepatic lipid accumulation in vivo. Raspberry ketone is a group of natural phenolic compounds in red raspberry [18]. Pure raspberry ketone is a translucent white short needle-like crystal powder, which is a class of natural phenolic compounds in red raspberry. Raspberry ketone and esters, aldehydes, alcohols, terpenes, ketones and pyrazines together form a complex mixture of volatile aroma components of red raspberries. Raspberry ketone can regulate body weight, prevent obesity, and alleviate obesity-induced hyperlipidemia in vivo [19]. Besides, raspberry ketones can increase insulin secretion and possesses hypoglycemic properties [20]. However, only a few studies have focused on the raspberry ketones extracted from red raspberry and determined their ability to modulate glucose and lipid metabolism to alleviate NAFLD. In the present study, we extracted and purified raspberry ketones from red raspberries and characterized their structure. We hypothesized that raspberry ketones from red raspberries can alleviate NAFLD. Moreover, we also investigated its effects in NAFLD model rats. We believe this study can provide a basis for the application of functional foods in the regulation and treatment of NAFLD.

Materials and methods

Materials and reagents

Red raspberry (*Rubus ideaus* L.) was obtained from ShangZhi District, Harbin City, Heilongjiang Province. AB-8 macroporous resin and polyamide resin were purchased from Macklin Reagent Company (Shanghai, China). Other reagents were of analytical grade.

Preparation of red raspberry ketones

Firstly, 20 g of red raspberry was added to 3000 mL of anhydrous ethanol (85%, v/v) and kept at 40 °C for 50 min for ultrasonic-assisted extraction. Afterward, the extract was purified by sequential elution using an AB-8 macroporous resin and polyamide resin. It was then freeze-dried under vacuum conditions to obtain purified red raspberry ketone (RRK).

Purity identification and structural characterization of RRK

The purity of RRK was determined by gas chromatography–mass spectroscopy (GC–MS). Briefly, RRK was dissolved in ethanol (0.1 mg/mL), and the GC–MS analysis conditions were as follows: An Agilent HP-5 (5%-phenyl)-methyl polysiloxane non-polar column with a hydrogen flame ionization detector (FID) was used. The injection port temperature was 250 °C, and the detector temperature was 280 °C. The column oven temperature was 220 °C, the carrier gas was N_2, and the split flow was 60:1, and the sample injection volume was 10 μL.[21].

The structure of RRK was detected by a Fourier transform infrared (FT-IR) spectrophotometer (Perkin-Elmer 2000, Perkin Elmer Company, USA) by KBr pressing method. The wavelength range was 500–4000 cm^{-1}.

Effect of RRK on NAFLD in vivo

Animals and treatments

A total of 64 specific pathogen-free Wistar rats (male, 220 ± 10 g) were purchased from the Changchun Yisi Experimental Animal Center (production license number, Scxk(Ji)-2011–0004; certificate number, 201,500,010,264) and kept at 23 ± 2 °C with a relative humidity of 40–70%. All the rats were provided with natural light and ad libitum access to food and water. After acclimatization for 7 days, 8 rats were selected in the control group (NC) and fed with a normal diet, whereas the remaining rats were fed with a high-fat diet. After continuous feeding for 28 days, the presence of heavy rats with serum levels of total triglyceride (TG) and total cholesterol (TC)

higher than those of the NC group was an indicator of successful modeling. Then, the NAFLD model rats were randomly divided into the following five groups: high fat model group (MC, n = 10 whose rats received intragastric administration of physiological saline solution), raspberry ketone high dose group (HRK, n = 10 whose rats received intragastric administration of RRK for 200 $mg{\cdot}kg^{-1}{\cdot}d^{-1}$), raspberry ketone medium-dose group (MRK, n = 10, whose rats received intragastric administration of RRK for 100 $mg{\cdot}kg^{-1}{\cdot}d^{-1}$), raspberry ketone low dose group (LRK, n = 10, whose rats received intragastric administration of RRK for 50 $mg{\cdot}kg^{-1}{\cdot}d^{-1}$), and positive control group (PC, n = 10, whose rats received intragastric administration of metformin for 150 $mg{\cdot}kg^{-1}{\cdot}d^{-1}$ and Tiopronin for 40 $mg{\cdot}kg^{-1}{\cdot}d^{-1}$). After 28 days of treatment, the rats in each group underwent fasting for 12 h. They were weighed and then sacrificed. The serum of the rats was extracted from the blood by centrifugation at 4 °C (3,000 rpm for 10 min). The liver tissue in each rat was also obtained and divided into two sections. One section was used for histopathological staining and the other section was homogenized for testing biochemical indicators [22, 23]. All procedures used in this experiment were approved by the Institutional Animal Care (the Animal Protection) and Use Committee of the Harbin University of Commerce.

Evaluation of biochemical parameters in the serum

The biochemical parameters, such as high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglyceride (TG), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AKP), glucose (GLU), free fatty acid (FFA) and tumor necrosis factor-α (TNF-α), in serum, were evaluated using standard kits (Nanjing Jiancheng Bioengineering Institute Co., Ltd, Nanjing, China).

Evaluation of biochemical parameters in the liver

The biochemical parameters, such as triglyceride (TG), malondialdehyde (MDA), superoxide dismutase (SOD), total glutathione (T-GSH), and glutathione peroxidase (GSH-Px), in the liver tissue was evaluated using standard kits (Nanjing Jiancheng Bioengineering Institute Co., Ltd, Nanjing, China).

Hematoxylin and eosin (H&E) staining of the liver

H&E staining was performed to determine the effect of raspberry ketones on liver histopathology in vivo. The fixed liver tissues were embedded, sectioned, stained, and sealed, and finally, each group of tissues was microscopically photographed.

Statistical analysis

The experimental data were analyzed using SPSS 17.0 software (SPSS, Chicago, IL, USA) for variance calculation and significance analysis. The data are expressed as mean ± standard deviation (mean ± SD), and the LSD method was performed for multiple comparisons between groups. All the figures were drawn using Origin 2018 (OriginLab Corp., MA, USA).

Results and discussion

Structure characterization of red raspberry ketones

The FT-IR spectra of RRK obtained by ultrasonic-assisted ethanol are shown in Fig. 1A We found that the spectrum of RRK was in line with the standard sample. We observed a strong and wide absorption peak at 3371.21 cm^{-1}, which was consistent with the characteristic absorption peak range of hydroxyl (3000–3750 cm^{-1}). We also observed an absorption peak around 1550 cm^{-1}, which was associated with a benzene ring. We inferred that a phenolic hydroxyl structure was present in RRK [24, 25].

The spectra of raspberry ketone standard obtained from GC–MS are shown in Fig. 1C The peak time of the standard was 4.685 min. The standard curve was $Y = 415.14X - 53.714$, $R^2 = 0.9990$ (Fig. 1B). As shown in Fig. 1C–D, the shape of the RRK chromatographic peak was similar to the raspberry ketone standard, and the peak time was 4.699 min. The purity of RRK was 80.06 ± 1.19%.

Effect of RRK on the biochemical indicators in serum

As shown in Fig. 2A, the body weight of rats in the high-fat diet group was significantly increased than those in the normal-diet group after they were fed for 4 weeks (260.12 ± 6.41 g vs 288.31 ± 16.60 g, $P < 0.01$). The HDL-C levels decreased remarkably, and the LDL-C, TC, and TG levels increased significantly ($P < 0.05$), which indicated that the NAFLD modeling was successful (Fig. 2B) [26].

During the administration period, the rats administered with RRK by oral gavage were more stable, moved freely, and had a better mental state and a shiny coat. Their diet and water intake were normal, and they did not show any abnormalities. However, the rats in the MC group which didn't administered with RRK had a darker and rougher coat because of the metabolic disorders in liver caused by NAFLD.

After 28 days of treatment, the body weight of rats in the MC group increased significantly ($P < 0.05$) than those in the NC group. The weight of rats in the PC, HRK, MRK, and LRK groups decreased significantly ($P < 0.05$) than those in the MC group. This indicated that RRK can decrease the body weight of NAFLD model

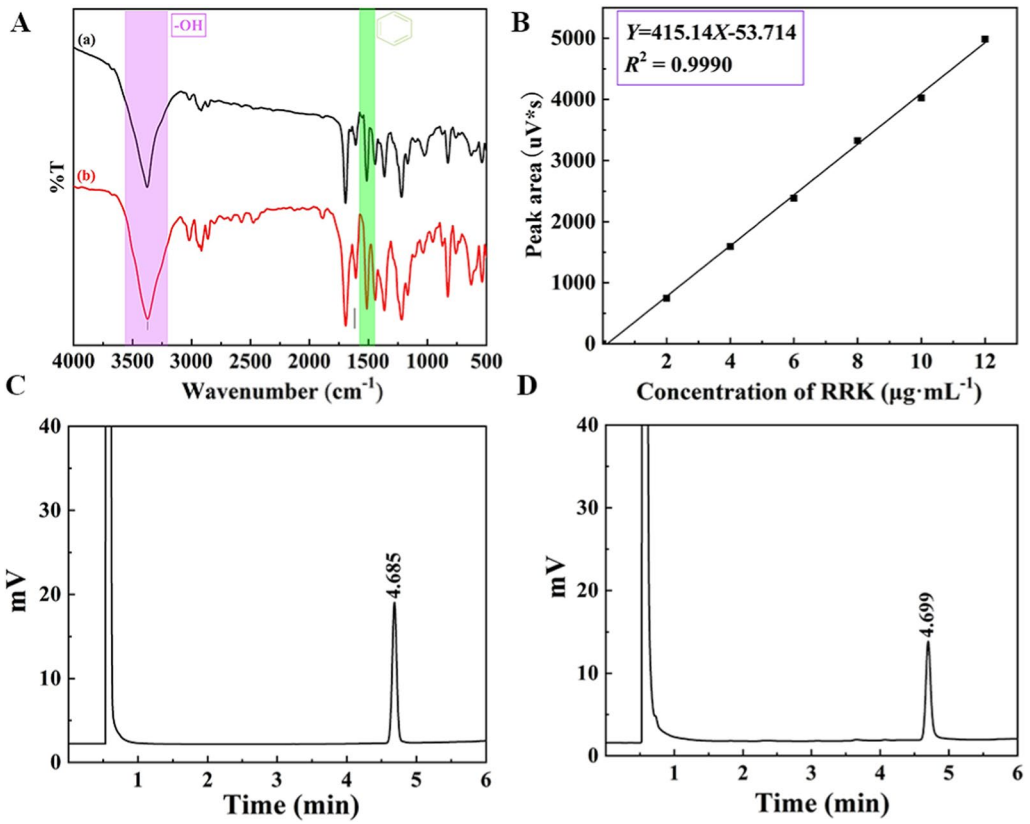

Fig. 1 Structure characterization of RRK. **A**: The Fourier transform infrared spectroscopy spectra of red raspberry ketone (RRK), **B**: Standard curve of raspberry ketone, **C**: Gas chromatogram of raspberry ketone standard (10 μg/mL), and **D**: Gas chromatogram of RRK (10 μg/mL)

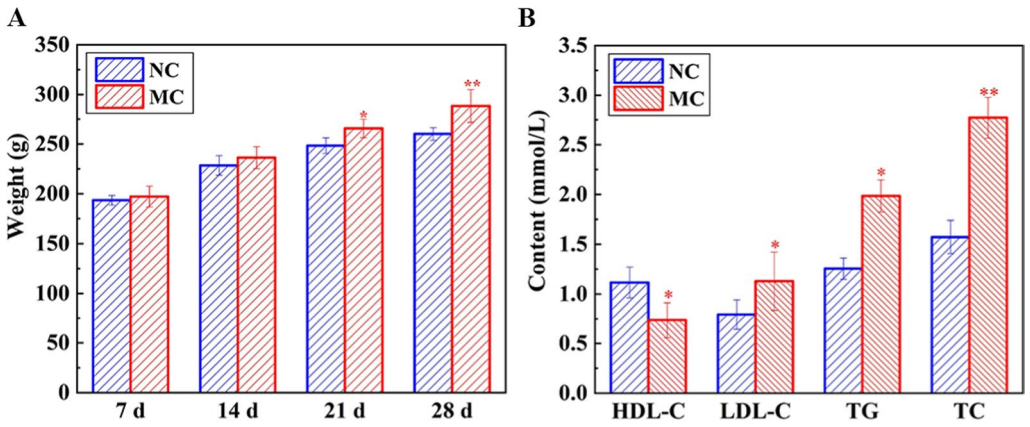

Fig. 2 Changes of rats after modeling. **A**: Changes in body weight after modeling; **B**: Changes in serum lipid level

rats (Fig. 3A). We also observed that the HDL-C levels of the NAFLD model rats increased, and the LDL-C, TC, and TG levels remarkably decreased after the treatment with RRK. (Fig. 3B–E, $P < 0.05$). This indicated that RRK can promote the breakdown and metabolism of lipids in the serum, and the ability to transport cholesterol and triglycerides was improved in the NAFLD model rats. Thus, RRK has a positive effect on the removal of the deposited lipids from the arterial wall of blood vessels.

Some studies have also found similar results. Reem et al. found Garcinia cambogia (Garcinia gummi-gutta) and raspberry ketone could alleviate hepatocyte

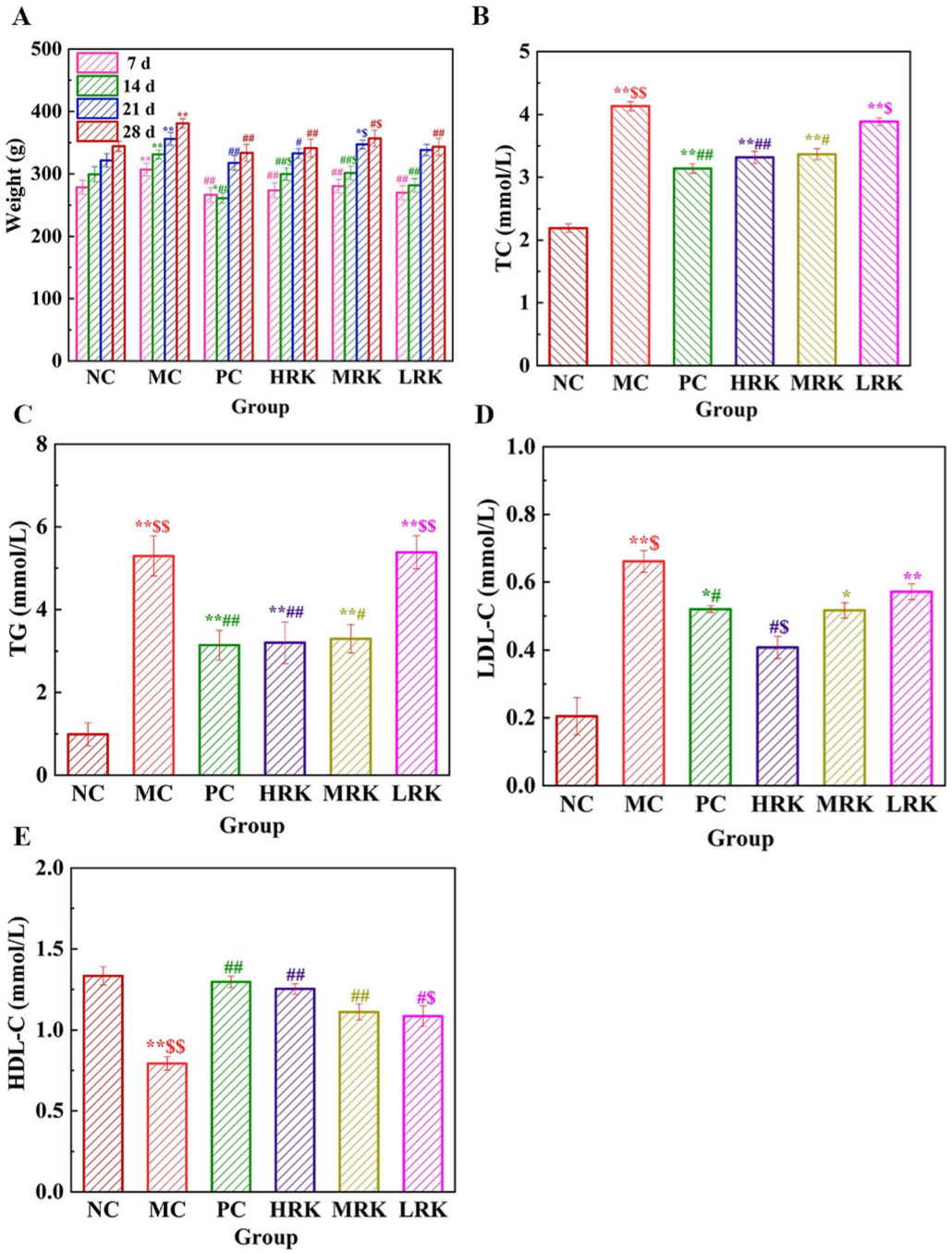

Fig. 3 Effect of red raspberry ketone (RRK) on body weight and the level of lipid biochemical indicators in serum. **A**: Effects of red raspberry ketone (RRK) on body weights of rats. **B**–**E**: Effects of RRK on TC (**B**), total triglyceride (TG) (**C**), low-density lipoprotein cholesterol (LDL-C) (**D**), and high-density lipoprotein cholesterol (HDL-C) (**E**) in serum of rats. (*P < 0.05, **P < 0.01 compared with NC; #P < 0.05, ##P < 0.01 compared with MC; $P < 0.05 compared with PC)

inflammation, fatty changes, and oxidative stress caused by a high-fat fructose diet [27]. Moreover, Wang et al. also found that raspberry ketone could protect the liver and reduce fat in the body against nonalcoholic steatohepatitis [28].

AST and ALT were released from the liver after its injury, which reflected the level of liver injury. As shown in Fig. 4A–B, the rats in the MC group showed a large increase in AST levels than those in the NC group (P < 0.01), whereas the AST levels decreased in the PC

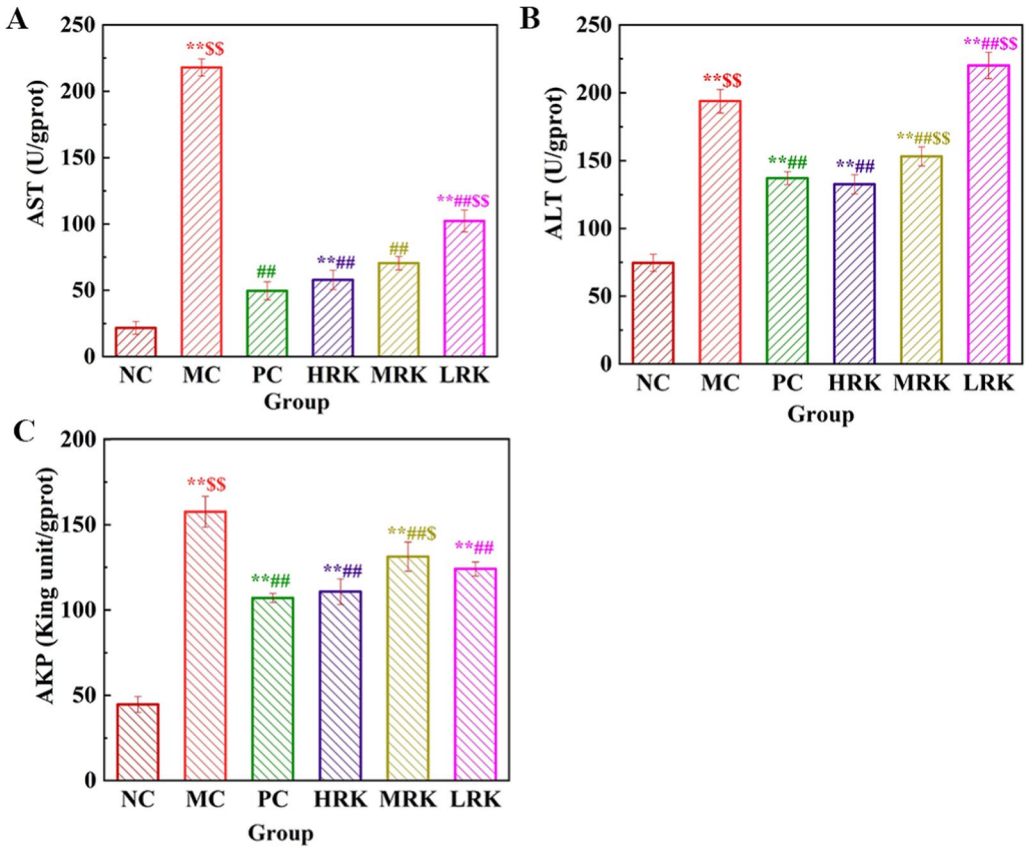

Fig. 4 Effect of red raspberry ketone (RRK) on the level of liver damage indicator in serum. **A**–**C**: Effects of red raspberry ketone (RRK) on aspartate aminotransferase (AST) **A**, alanine aminotransferase (ALT) **B** and alkaline phosphatase (AKP) **C** in serum of rats. (*P < 0.05, **P < 0.01 compared with NC; #P < 0.05, ##P < 0.01 compared with MC; $P < 0.05 compared with PC)

and RRK groups than those in the MC group (P < 0.01). Moreover, the ALT levels in the MC group also exhibited a remarkable improvement compared with those in the normal group (P < 0.01), whereas the ALT levels in the PC and RRK treatment groups, showed a highly significant decrease compared with those in the MC group (P < 0.01). Thus, RRK can decrease the levels of ALT and AST in serum. We inferred that RRK may repair necrotic hepatocytes to a certain extent and might be able to decrease the permeability of the cell membrane. Overall, RRK can inhibit the further development of NAFLD, which has certain significance in its clinical prevention. These results are consistent with some previous studies. Faheem et al. reported that cranberry extract can decrease ALT and AST levels in serum and can retard the progression of NAFLD [14]. The extract from pomegranate peel can decrease the levels of ALT and AST and can be used in the treatment of NAFLD [29]. AKP is overproduced when the liver cells are damaged. Compared with the NC group, the AKP level in the MC group significantly increased (P < 0.01), and the AKP level in the PC group and the groups with different doses of RRK significantly decreased (Fig. 4C, P < 0.01) compared with the MC group. This indicated that RRK can effectively reduce AKP levels in serum and control the abnormal metabolism and impaired excretion of AKP from the body. These results were consistent with those of other studies [30, 31]. Hence, the results showed that RRK can prevent the inflammatory response in the liver to alleviate NAFLD.

Some studies have reported that abnormal lipid metabolism can trigger an increase in the blood glucose levels of the body and insulin resistance can be present, which can contribute to the risk of type 2 diabetes such as Shah et al.'s and Koh et al.'s studies [32, 33]. Based on this, we speculated that RRK can decrease glucose levels. We found that the glucose levels in the MC group increased significantly compared with those in the NC group (P < 0.01), and the model rats treated with different doses of RRK had decreased glucose levels in the serum, which was consistent with the results of the PC group. The results indicated that RRK can inhibit the secretion of blood glucose in vivo (Fig. 5A). Insulin (INS)

is a major hormone that lowers blood glucose levels and promotes glycogen synthesis. An abnormal increase in blood glucose levels leads to an increase in the compensatory secretion of INS. The levels of INS increased significantly in the MC group, and this phenomenon was relieved remarkably in the RRK group in a dose-dependent manner (Fig. 5B, $P < 0.05$). This finding is consistent with those of other studies. A plant extract, procyanidin B2, can improve insulin resistance and glucose–lipid metabolism during NAFLD and reduce blood glucose levels [34]. You et al. also reported that oat β-glucan can relieve abnormal lipid metabolism, which was associated with a decrease in blood glucose levels [35]. In this study, we found that RRK can decrease the glucose and insulin levels in rats, which indicated that RRK can also increase glucose metabolism in vivo. Therefore, we hypothesized that RRK also has a positive effect on diabetes.

FFA concentration in the blood serum is associated with the glycolipid metabolism and endocrine function in vivo and indicates the degree of liver injury. Figure 5C showed that FFA levels were significantly higher in the MC group than those in the NC group ($P < 0.01$) and were significantly lower in the rats treated with RRK, which was similar to the results of the PC group. High FFA can cause an inflammatory response, which in turn leads to metabolic disturbances in the body. TNF-α is an important indicator of the inflammatory response, which was significantly higher in the MC group than in the normal rats ($P < 0.01$). After RRK treatment, TNF-α levels in serum indicated a significant decrease (Fig. 5D, $P < 0.05$). These results suggested that RRK can decrease the production of TNF-α in the adipose tissue. Ngamlerst et al. reported that Maoberry extracts decreased TNF-α levels in the NAFLD model rats and decreased lipid production [36]. A previous study reported that excessive FFA leads to the overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS) [37]. Some studies reported that the increased indicators of the inflammatory response can induce oxidative stress in vivo [38, 39]. We speculated that RRK has a positive effect on lipid metabolism, oxidative stress, and inflammatory response in the liver tissues.

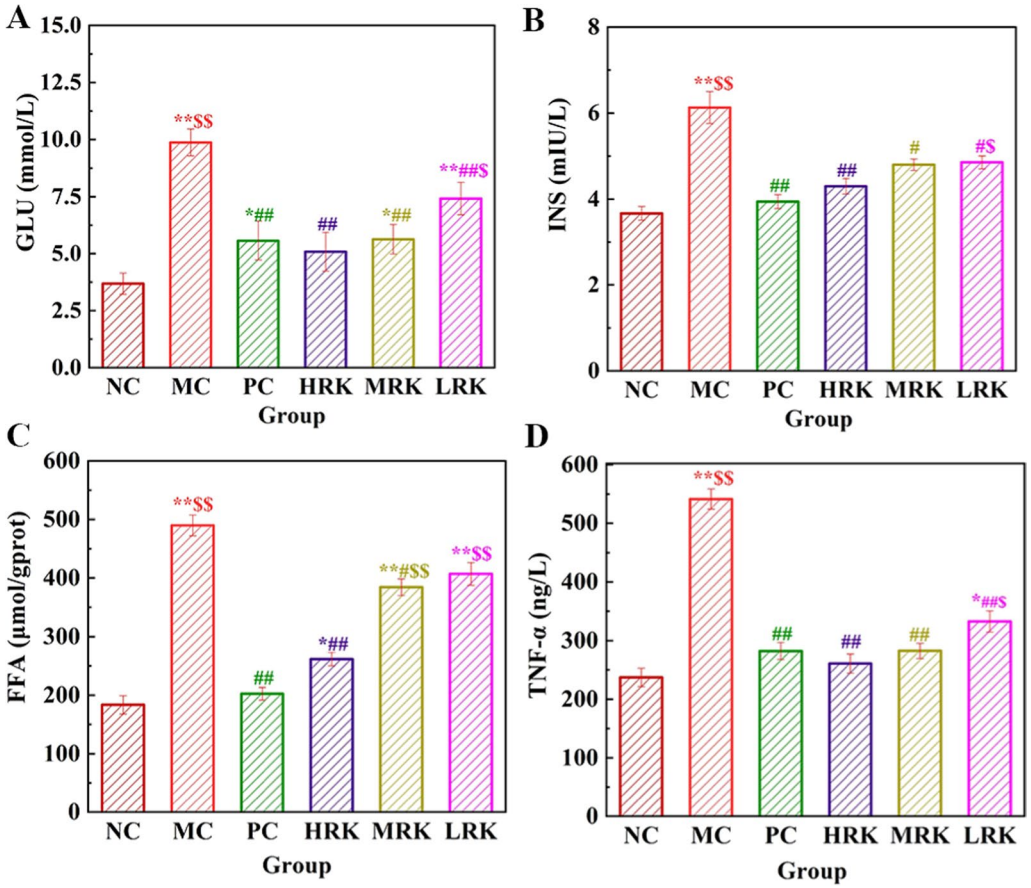

Fig. 5 Effect of red raspberry ketone (RRK) on the level of glucose (GLU) **A**, insulin (INS) **B**, free-fatty acid (FFA) **C**, and tumor necrotic factor (TNF)-α **D** in serum. *$P < 0.05$, **$P < 0.01$ compared with NC; #$P < 0.05$, ##$P < 0.01$ compared with MC; \$$P < 0.05$ compared with PC

Effect of RRK on the biochemical indicators in the liver

Figure 6A shows some representative indicators of lipid metabolism. Compared with the NC group, the TG levels in the liver were significantly higher in the MC group ($P < 0.01$), whereas it was markedly decreased ($P < 0.01$) in the PC, HRK, MRK, and LRK groups. This also showed a certain dose–effect relationship. It indicated that RRK can effectively inhibit

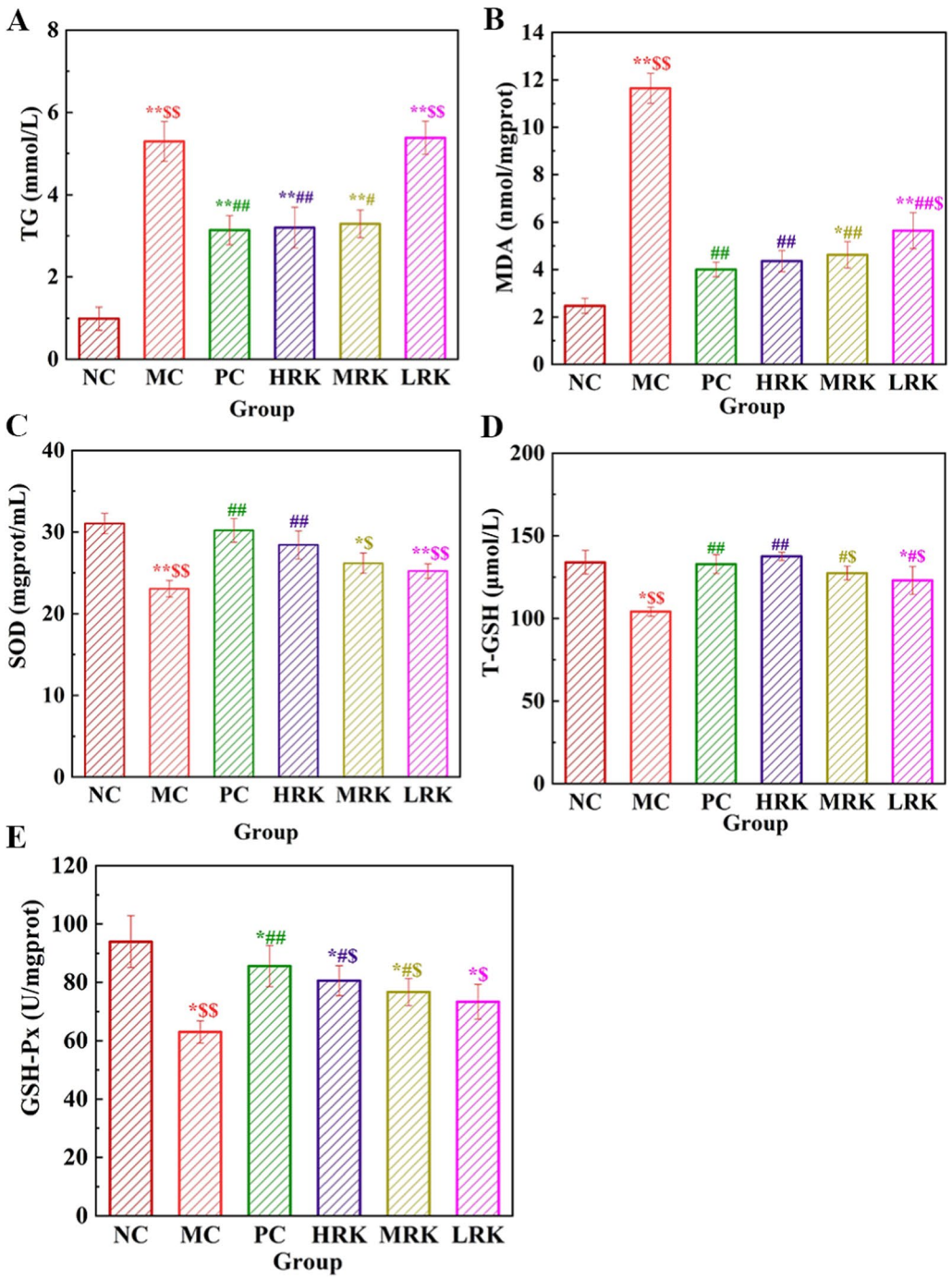

Fig. 6 Effect of red raspberry ketone (RRK) on biochemical indicators in liver. **A**–**E**: Effects of red raspberry ketone (RRK) on total triglyceride (TG) **A**, malondialdehyde (MDA) **B**, superoxide dismutase (SOD) **C**, total glutathione (T-GSH), **D** and glutathione peroxidase (GSH-Px) (E) in the serum of rats. (*$P < 0.05$, **$P < 0.01$ compared with NC; #$P < 0.05$, ##$P < 0.01$ compared with MC; \$$P < 0.05$ compared with PC)

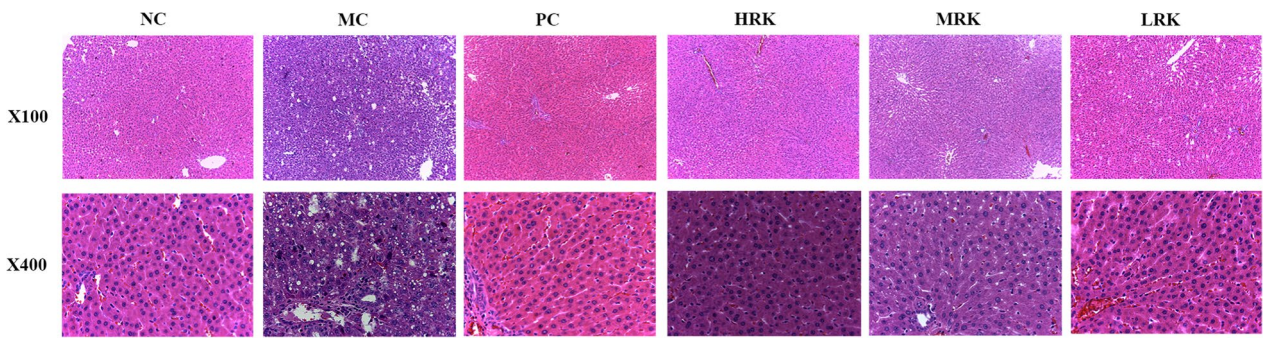

Fig. 7 Hematoxylin and eosin (HE) staining results of the liver tissue of rats in each group

the increase of TG and maintain lipid metabolism in the liver of NAFLD rats. This result was consistent with the results of some previous studies [40, 41].

To determine whether RRK can alleviate oxidative stress to relieve NAFLD, we evaluated the levels of MDA, SOD, T-GSH, and GSH-Px to determine the antioxidant capacity of the liver (Fig. 6B–E). MDA is a product of lipid peroxidation in the body, which can reflect the degree of lipid peroxidation. This is an indicator of cell damage and biofilm destruction. We found a remarkable increase in the MDA level of the MC group ($P < 0.01$), which decreased significantly after RRK treatment compared with that of the model group ($P < 0.01$). Meanwhile, the level of SOD in the serum of the MC group decreased significantly ($P < 0.01$), which indicated that the ability of NAFLD rats to remove harmful substances decreased during the metabolic process. The level of SOD in the liver increased distinctly after RRK treatment than those in the model group ($P < 0.01$). Glutathione (T-GSH) is an important antioxidant and free radical scavenger in living organisms. It can bind to harmful substances, such as free radicals and heavy metals and help in their excretion. Glutathione peroxidase (GSH-Px) can decompose lipid hydroperoxides in organisms and inhibit the damage of fatty acids on biofilms. RRK can significantly increase the GSH and GSH-Px levels in NAFLD rats. This suggested that RRK can repair cell damage and biofilm disruption triggered by abnormal lipid metabolism caused by NAFLD. All these findings showed that RRK can improve the antioxidant capacity of NAFLD rats in the liver. Denise et al. reported that the extract of *Citrus maxima* leaves showed antioxidant activity in the NAFLD model rats, which was consistent with the results of our study [42]. Furthermore, we also speculated that RRK can also have a positive effect on liver morphology.

Morphological observations of the liver

The results of liver pathology staining are shown in Fig. 7. The hepatic tissues of the NC group have a clear and intact structure, along with a certain regularity of cell arrangement and distribution, normal size of hepatocytes, medium-sized nuclei, and a more homogeneous cell body. In the MC group, we observed that the lobules of the liver were heavily damaged, and most cells varied markedly in size and contained a certain amount of lipid droplet vacuolation within the hepatocytes, along with steatosis and fibrosis. Moreover, we observed varying degrees of cellular inflammation with focal necrosis of the glandular follicles, which is consistent with the liver inflammation indicators. After treatment with RRK, the liver lobules were clearer, the hepatic blood sinusoids were more intact, and the hepatic cords were more regularly arranged. We observed no distinct steatosis or inflammatory infiltration. The hepatocytes were more regularly arranged, and fewer intrahepatic lipid droplets were observed in the HRK group. Also, the hepatic cords were more distinctly defined, and the structural integrity of the hepatic lobules was improved more remarkably. These findings were consistent with those of some other reports [43, 44]. These results indicated that RRK has positive therapeutic effects on NAFLD in a dose-dependent manner.

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Author contributions

YQM and XW led the project, designed the study, interpreted the results, and revised the paper; WYX and QHY produced the experiments and collected the data; XW and WYX performed the data analyses and wrote the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

All data, models, and code generated or used during the study appear in the submitted article. The data presented in this paper are available on request from the first author and corresponding author.

Declarations

Competing interests

All authors state that they have no personal or financial conflicts of interest.

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