Effects of *Sporisorium reiliana* polysaccharides and *Phoenix dactylifera* monosaccharides on the gut microbiota and serum metabolism in mice with fructose-induced hyperuricemia

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**Abstract**

In recent decades, the prevalence of hyperuricemia has increased, and dietary fructose is an important risk factor for the development of this disease. This study investigated and compared the effects of *Sphacelotheca reiliana* polysaccharides and *Phoenix dactylifera* monosaccharides on a series of physiological and biochemical indicators and on the metagenomes and serum metabolites in mice with hyperuricemia caused by a high-fructose diet. *S. reiliana* polysaccharides inhibited uric acid biosynthesis and promoted uric acid excretion, thereby alleviating the hyperuricemia phenotype. In addition, hyperuricemia was closely related to the gut microbiota. After treatment with *S. reiliana* polysaccharides, the abundances of Bacteroidetes and Proteobacteria in the mouse intestines were decreased, the expression of genes involved in glycolysis/gluconeogenesis metabolic pathways and purine metabolism was downregulated, and the dysfunction of the gut microbiota was alleviated. With regard to serum metabolism, the abundance of hippuric acid, uridine, kynurenic acid, propionic acid and arachidonoyl decreased, and the abundances of serum metabolites in inflammatory pathways involved in kidney injury and gout, such as bile acid metabolism, purine metabolism and tryptophan metabolism pathways, decreased. *P. dactylifera* monosaccharides aggravated hyperuricemia. This research provides a valuable reference for the development of sugar applications.

**Keywords** *Sphacelotheca reiliana* polysaccharide · *Phoenix dactylifera* monosaccharide · Fructose · Hyperuricemic · Metagenomics · Metabolomics

**Introduction**

Hyperuricemia (HUA) is a metabolic state characterized by elevated serum urate (SU) that has been confirmed to be caused by abnormal purine metabolism, and urate is the main product of purine metabolism (Lu et al. 2020). Studies have shown that long-term consumption of fructose can inhibit renal uric acid excretion, leading to increased serum uric acid levels, and the global prevalence of hyperuricemia has increased significantly (Zgaga et al. 2012). The current drug therapy has strong side effects, so it is necessary to find natural active substances to relieve hyperuricemia given the trend of high-fructose consumption in the diet (Stewart et al. 2019).

*Sphacelotheca reiliana* is a fungus with good nutritional and medicinal value that is responsible for head smut disease in sorghum (Prom et al. 2021). Through the study of its components, it has been found that this fungus contains rich active ingredients that can be used as functional foods.
to produce biologically active substances such as proteins, vitamins, polysaccharides and minerals. It has good nutritional and medicinal value. Fungal polysaccharides are natural macromolecular compounds derived from the fruit bodies or mycelia of fungi. With the continuous deepening of polysaccharide research, it has gradually been discovered that polysaccharides from different plant sources have antiviral properties, anticancer immune-regulating effects, blood sugar-lowering and blood fat-lowering effects, anti-aging effects and many other functions (Kimura et al. 2006; Yu et al. 2018). Therefore, polysaccharides have been developed into a variety of drugs and food additives (such as lentinan, Hericium polysaccharides, Ganoderma lucidum polysaccharides, brown seaweed polysaccharides, white fungus polysaccharides and black fungus polysaccharides). At present, there is much research on the planting, preservation and storage of S. reiliana, but there have been few domestic studies on its functions. P. dactylifera has long been one of the most important fruit crops in the arid regions of the Arabian Peninsula, North Africa, and the Middle East (Abdelhak et al. 2005). Phoenix dactylifera varieties are rich in sugar, fiber and minerals (potassium, magnesium and calcium), and the content of fructose is as high as 90%, but P. dactylifera has a low content of protein, amino acids (methionine, tyrosine and phenylalanine) and lipids (Assirey 2015). In addition, it is rich in phenols, flavonoids, carotenoids, etc., and has antioxidant, antimutagenetic and medicinal value (Tang et al. 2013). At present, there are few studies on the relationship between P. dactylifera and fructose-induced hyperuricemia. Therefore, S. reiliana and P. dactylifera were selected to explore the differences in the activity and function of their polysaccharides and monosaccharides from the perspectives of physiology, biochemistry, microbiota and serum metabolism.

The gut microbiome contains nearly 100 trillion interdependent microorganisms, which include bacteria, fungi, viruses and protozoa that participate in the maintenance and maturation of the immunological system, metabolism and other processes to ensure homeostasis (Zhao et al. 2021). Uric acid is the end product of purine or nucleotide metabolism, of which 2/3 is excreted by glomerular filtration and 1/3 is excreted through the intestine (Johnson et al. 2018). Several studies have found an altered gut microbiome in gout patients and supported the hypothesis that the gut microbiota participates in the metabolism of purines and uric acid (Liu et al. 2020). In addition, the modulation effects of the gut microbiota by dietary factors have been widely reported; thus, the underlying mechanism of how dietary factors alleviate the disease was clarified as it relates to the gut microbiota (Xu et al. 2021).

Among serum metabolites, there are many biomarkers and substances that cause various diseases. Some specific compounds are endogenous, including metabolites that are strongly inherited or influenced by gut microbes and others that are influenced by lifestyle factors (Marchand et al. 2016). Fructose-induced hyperuricemia is also related to metabolite changes. After consumption of a large amount of fructose, a series of enzymes induce changes during fructose metabolism and transformation, leading to abnormal uric acid metabolism and changes in various metabolic indicators; metabolic syndrome even occurs in severe cases. Compared with individuals without hyperuricemia, patients with hyperuricemia have different changes in the intestinal microflora and serum metabolites.

It is of great practical significance for early clinical prevention and treatment to select animal models that exhibit uric acid metabolism similar to the abnormal uric acid metabolism caused by an excessively high-fructose diet in humans and to carry out antagonist studies on bioactive substances against hyperuricemia. In the present study, a fructose-induced hyperuricemia mouse model was treated with S. reiliana polysaccharide and P. dactylifera monosaccharide diets, and a series of analyses were conducted on the physiological and biochemical variables, transcription levels, metagenomes and serum metabolite data of the mice.

**Materials and methods**

**Extraction of monosaccharides and polysaccharides**

*Sphacelotheca reiliana* was purchased from the professional farmer cooperative of Lishu County (Siping City, Jilin Province, China). The fruit bodies of *S. reiliana* are crushed. The *S. reiliana* was soaked in 75% ethanol for 24 h to remove hydrophobic compounds, such as lipids. After filtration, the residue was dried at room temperature (25°C) and treated with hot distilled water 3 times (95°C, 1:20 w/w, 6 h), and the resulting polysaccharide extract was mostly sticky. The filtrate was then filtered, combined, and concentrated by rotary evaporation at 60°C. The water extract was centrifuged at 8000 rpm for 5 min, and the supernatant was precipitated with an 80% final concentration of ethanol solution at 4°C for 24 h. The precipitate was then obtained by centrifugation at 3000 rpm for 15 min and washed with anhydrous ethanol, acetone and ether 3 times. Finally, the *S. reiliana* polysaccharides were obtained by freeze-drying.

To extract the *P. dactylifera* monosaccharide, the raw material was obtained from King Abdullah University of Science and Technology (Jeddah, Saudi Arabia). First, the *P. dactylifera* was boiled at 85–90°C for 10 min, crushed in the liquid state and dried at low temperature. An aqueous ethanol solution with a pH value of 1.0–3.0 and a mass fraction of 65–85% was added for 4–6 h of extraction at 30–60°C and concentrated by rotary evaporation at 60°C. After filtration, the filtrate was collected and concentrated.
to obtain the *P. dactylifera* fructose extract. Finally, the *P. dactylifera* polysaccharides were obtained by freeze-drying. The extracted *S. reiliana* and *P. dactylifera* were taken to Microspectrum Technology Co., Ltd. (Shanghai, China) for composition testing.

**Experimental design**

All experimental procedures and animal care were performed in accordance with the Guide for the Care and Use of Laboratory Animals prepared by the Ningbo Customs Technology Center (affiliated with the Zhejiang Laboratory Animal Common Service Platform), and all of the animal protocols were approved by the Ningbo Customs Technology Center under permit number SYXK (ZHE 2018-0003).

Fifty-six eight-week-old SPF C57BL/6 male mice (21.91 ± 1.19 g) were purchased from Ziyuan Experimental Animal Science Technology Co., Ltd. (Hangzhou, Zhejiang, China) under license SCXK (Zhejiang) 2019-0004 (number: 1911070205). The animals were housed in a controlled environment at 25 °C under a 12-h light/12-h dark cycle with free access to food. The mice were fed a standard chow diet purchased from Ningbo Customs Technology Center. After 1 week of acclimatization, the mice were randomly assigned to 7 groups, with eight mice per group: a blank control (CT) group, a high-fructose model (HF) group, an allopurinol-treated (HF + AL) group, a low-dose *S. reiliana*-treated (HF + UL) group, a high-dose *S. reiliana*-treated (HF + UH) group, a low-dose *P. dactylifera*-treated (HF + DL) group and a high-dose *P. dactylifera*-treated (HF + DH) group; all of the mice within a cage were from the same group. Except for the CT group, which was given normal drinking water, the other groups were all given 13% fructose solution for 8 weeks. The mice in the CT group and HF group received 200 μL of saline by oral gavage once a day. The mice in the HF + AL group were administered 20 mg·kg⁻¹ day⁻¹ allopurinol by gavage, while the mice in the other groups (the HF + UL, HF + UH, HF + DL and HF + DH groups) received 50 mg·kg⁻¹ day⁻¹ *S. reiliana*, 100 mg·kg⁻¹ day⁻¹ *S. reiliana*, 50 mg·kg⁻¹ day⁻¹ *P. dactylifera* or 100 mg·kg⁻¹ day⁻¹ *P. dactylifera* by gavage for 8 weeks (Fig. S1). These dosages were chosen based on previous literature (Kamatani et al. 2008; Luo 2021; Jiang 2013). The choice of dose, which was chosen based on previous studies, was equivalent to a dose of 729.6 mg day⁻¹ in a 60-kg human (Reagan-Shaw et al. 2008).

Body weight was measured every week. On the last day of the experiment, urine and stool samples were collected from each mouse and stored at −80 °C. After the mice were anesthetized with isoflurane, blood samples were obtained from the eye sockets, and serum was separated via centrifugation for 10 min at 4 °C at 3500 rpm and stored at −80 °C for biochemical tests. The mice were sacrificed by cervical dislocation, and their visceral organs were excised, weighed, and immediately stored at −80 °C until further analysis.

**Glucose tolerance test**

After they were raised for 8 weeks, the mice were fasted for 12 h. First, the fasting blood glucose of the mice was measured by taking blood from the tail vein and recorded as the 0-min blood glucose. Then, glucose was injected into the abdominal cavity of each mouse at a dose of 0.5 g kg⁻¹. The blood glucose level was measured 30 min, 60 min, and 120 min after glucose administration, and a glucose curve was drawn.

**Measurement of biochemical indices**

The uric acid (C012-2-1), creatinine (C011-2-1), and urea nitrogen (C013-2-1) levels were determined according to the instructions of the kits (Nanjing Jiancheng Bioengineering Institute, Nanjing, Jiangsu, China).

**Quantitative real-time PCR (qPCR)**

RNA extraction and qPCR analysis were performed according to previously described methods (Huang et al. 2019). The liver and kidney were first homogenized in liquid nitrogen, following by use of the TransZol Up Plus RNA Kit and TransScript All in-One First-Strand cDNA Synthesis SuperMix Kit (TransGen Biotech, Beijing, China) for RNA extraction and cDNA synthesis. A Rotor-Gene 6000 real-time PCR instrument (Corbett Robotics Inc., Sydney, Australia) with SYBR® Premix Ex Taq™ II was used to perform qRT–PCR, according to the manufacturer’s protocol. Each sample was measured in triplicate in a 20-μL total reaction volume (10 μL of SYBR Premix Ex Taq™ III mixture, 1.6 μL of 10 μM primer pairs, 2 μL of cDNA template, and 6.4 μL of RNase-free ddH2O). The qRT–PCR method was designed as follows: 95 °C for 10 min, followed by 40 cycles of 95 °C for 10 s, 55 °C for 10 s, and 72 °C for 20 s. The endogenous control β-actin was used to normalize the PCR products in mouse tissues, and their levels were calculated using the 2⁻ΔΔCT method. The qPCR primers used in this study are presented in Table S1. β-Actin was used as an internal control (Livak and Schmittgen 2001).

**Metagenomic sequencing**

Fecal samples collected on the last day of animal experiments were used for metagenomic sequencing. Total DNA from stool samples was extracted using the E.Z.N.A.® Fecal DNA Kit (D4015, Omega, Inc., USA) followed by use of the instructions of manufacturer, which was eluted in 50 μL of buffer and quantified by LC-Bio Technology Co.,
Ltd., Hangzhou, Zhejiang Province, China. Finally, 1.2% agarose gel electrophoresis was used for confirmation of the DNA extracts. The DNA library was constructed by a TrueSeq Nano DNA LT Library Preparation Kit (FC-121-4001). DNA was fragmented by dsDNA Fragmentase (NEB, M0348S) by incubation at 37 °C for 30 min. Library construction began with fragmented DNA. Blunt-end DNA fragments were generated using a combination of fill-in reactions and exonuclease activity, and size selection was performed with the provided sample purification beads. An A-base was then added to the blunt ends of each strand, preparing them for ligation to the indexed adapters. Each adapter contains a T-base overhang for ligating the adapter to the A-tailed fragmented DNA. These adapters contain the full complement of sequencing primer hybridization sites for single, paired-end, and indexed reads. Single- or dual-index adapters were ligated to the fragmented DNA. The adapters contain the full complement of sequencing primer hybridization sites for single, paired-end, and indexed reads. Single- or dual-index adapters were ligated to the fragments, and the ligated products were amplified with PCR by the following conditions: initial denaturation at 95 °C for 3 min; 8 cycles of denaturation at 98 °C for 15 s, annealing at 60 °C for 15 s, and extension at 72 °C for 30 s; and then a final extension at 72 °C for 5 min. Metagenomic shotgun sequencing was performed using an Illumina HiSeq 4000 (Illumina, Inc., San Diego, CA, USA) (Wang et al. 2019) at Lc-Bio Technologies Co., Ltd. (Hangzhou).

Raw sequencing reads were processed to obtain valid reads for further analysis. First, sequencing adapters were removed from sequencing reads using cutadapt v1.9. Second, low-quality reads were trimmed by fqtrim v0.94 using a sliding-window algorithm. Third, reads were aligned to the host genome using Bowtie2 to remove host contamination. Once quality-filtered reads were obtained, they were de novo assembled to construct the metagenome for each sample by IDBA-UD. All coding regions (CDSs) of metagenomic contigs were predicted by MetaGeneMark v3.26.

The CDSs of all samples were clustered by CD-HIT v4.6.1 to obtain unigenes. Unigene abundance for a certain sample was estimated by TPM based on the number of aligned reads by bowtie2 v2.2.0. The lowest common ancestor taxonomy of unigenes was obtained by aligning them against the NCBI NR database by DIAMOND v0.7.12. Similarly, the functional annotation (GO, KEGG, eggnog, CAZy, CARD, PHI) of unigenes was obtained. Based on the taxonomic and functional annotation of unigenes, along with the abundance profile of unigenes, differential analysis was carried out at each taxonomic, functional or genewise level by Fisher’s exact test (non-replicated groups) or the Kruskal–Wallis test (replicated groups). The sequence was deposited in the NCBI Sequence Read Archive Database under the accession number PRJNA785116.

Serum metabolite detection

Twenty microliters of serum was added to 120 μL of 50% methanol, shaken and mixed thoroughly, and the mixture was allowed to stand for 10 min at room temperature. The mixture was extracted overnight at − 20 °C to precipitate the protein in the serum. After centrifugation, the supernatant metabolite extract was transferred to a 96-well plate. Finally, 10-μL volumes from each sample were mixed into quality control (QC) samples. Metabolic profiling analysis of the tissues was conducted on an ultra-performance liquid chromatography (UPLC) system (SCIEX, Warrington, UK) with an ACQUITY UPLC T3 column (100 mm 2.1 mm, 1.8 μm, Waters, London, UK). The Q-TOF was operated separately in both the electrospray ionization-positive (ESI+) and electrospray ionization-negative (ESI) modes. The sequencing was completed by Lc-Bio Technologies Co., Ltd. (Hangzhou).

Statistical analysis

The data are shown as the means ± standard deviations (SDs). Using SPSS 20.0 software, one-way analysis of variance (ANOVA) was used to analyze the significant differences between the groups. The data that conformed to a normal distribution were analyzed by ANOVA and Tukey’s post hoc test, and the data that did not meet the assumptions of the ANOVA were analyzed by the Mann–Whitney test (Dasilva et al. 2016). GraphPad Prism 7 was used for mapping, and t tests and one-way ANOVA were used for comparisons between groups. Differences were considered statistically significant when \( p < 0.05 \).

Results

Composition of S. reiliana polysaccharides and P. dactylifera monosaccharides

The chromatogram of the monosaccharide composition is provided in Fig. S2. Among the monosaccharide components of the extracted S. reiliana polysaccharides, the glucose content was the highest, reaching 55.52%. The levels of mannose and galactose were 2% and 0.67%, respectively (Table S2). In the extracted P. dactylifera monosaccharides, the glucose content was as high as 49.25%, the galacturonic acid content was 0.58%, the proportion of rhamnose monohydrate was 0.52%, and the content of mannose was 0.45% (Table S3).
Physiological and biochemical indices of hyperuricemic mice

As shown in Fig. S3a, the effects of polysaccharides and monosaccharides that have an effect on glucose homeostasis in high-fructose diet-fed mice were evaluated by intraperitoneal glucose tolerance tests. After the mice were injected with glucose in the abdominal cavity, the blood glucose level of each group reached the highest value at 30 min and returned to the initial level at 60 min. The lowest fasting blood glucose level was 6.43 ± 0.64 in the CT group, and the maximum change was 13.18 ± 0.55 at 30 min. The fasting blood glucose level in the HF group was 10.28 ± 0.80, and the change was 14.03 ± 2.03 at 30 min. The blood glucose levels of the HF + AL, HF + UL and HF + UH groups showed little change, while those of the HF + DL group and HF + DH group did not change significantly. During the experiment, the mice in the CT group gained the most weight, with weight gain reaching 4.68 g; the mice in the HF + DH monosaccharide group gained the least weight at approximately 3.98 g (Fig. S3b). Through statistical analysis of the organ indices of the liver and kidneys, it was found that the liver index and kidney index values were reduced in the HF + UL group. The liver index and kidney index of the HF + AL group were the highest, but there were no significant differences (p > 0.05) (Fig. S3c).

The levels of serum uric acid (174.39 ± 20.63 μmol L^{-1}, p < 0.001), liver uric acid (829.76 ± 101.09 μmol L^{-1}, p < 0.05), urine uric acid (172.96 ± 13.33 μmol L^{-1}, p < 0.01), and fecal uric acid (247.69 ± 146.80 μmol L^{-1}, p < 0.01) in the HF group were significantly higher than those in the CT group. Compared to the HF group, the HF + AL group exhibited significantly lower serum uric acid (99.70 ± 18.98 μmol L^{-1}, p < 0.001), liver uric acid (584.40 ± 87.36 μmol L^{-1}, p < 0.01), urine uric acid (113.58 ± 8.41 μmol L^{-1}, p < 0.001) and fecal uric acid (420.70 ± 34.14 μmol L^{-1}, p < 0.001) levels. Serum uric acid (125.71 ± 14.65 μmol L^{-1}, p < 0.001), liver uric acid (604.07 ± 8.81 μmol L^{-1}, p < 0.01) and urine uric acid (118.57 ± 13.11 μmol L^{-1}, p < 0.001) levels were decreased significantly in the HF + UL group. Fecal uric acid (1735.83 ± 266.44 μmol L^{-1}, p < 0.01) levels were increased significantly in the HF + UH group, but there were no significant differences in uric acid in the other groups. In the HF + DL group, serum uric acid (129.87 ± 20.72 μmol L^{-1}, p < 0.01), liver uric acid (683.91 ± 73.11 μmol L^{-1}, p < 0.05), and urine uric acid (129.87 ± 20.72 μmol L^{-1}, p < 0.01) were decreased significantly, and fecal uric acid (1643.63 ± 237.70 μmol L^{-1}, p < 0.01) was increased significantly. In the HF + DH group, serum uric acid (183.71 ± 17.26 μmol/L), liver uric acid (854.20 ± 60.14 μmol L^{-1}), and urine uric acid (172.80 ± 6.46 μmol L^{-1}) were not significantly different (p > 0.05), while fecal uric acid (1902.22 ± 224.06 μmol L^{-1}) was increased significantly (p < 0.01). (Fig. 1A).

Compared with those in the CT group, the mice in the HF group had significantly higher serum creatinine (56.30 ± 6.79 μmol/L, p < 0.001), blood urea nitrogen (24.84 ± 3.45 mmol L^{-1}, p < 0.001) and urine urea nitrogen (330.90 ± 67.83 mmol/L, p < 0.01) contents. Compared with those in the HF group, the mice in the HF + AL group had significantly lower serum creatinine (38.68 ± 2.71 μmol/L, p < 0.001) and blood urea nitrogen (16.99 ± 1.92 mmol/L, p < 0.001) levels but a significantly higher urine urea nitrogen content (566.57 ± 140.19 mmol/L, p < 0.01). Compared with levels in the HF group, serum creatinine (43.47 ± 3.31 μmol/L, p < 0.001), blood urea nitrogen (18.02 ± 3.36 mmol/L, p < 0.01) and urine urea nitrogen (489.11 ± 28.75 mmol/L, p < 0.001) were significantly increased in the HF + UL group. Compared with levels in the HF group, urinary urea nitrogen was significantly increased in the HF + UH group (549.18 ± 90.05 μmol/L, p < 0.001). Compared with levels in the HF group, serum creatinine (41.91 ± 3.10 μmol/L, p < 0.001) and blood urea nitrogen (20.37 ± 3.61 mmol/L, p < 0.05) in the HF + DL group were increased significantly. Compared with the HF group, there were no significant differences in several indices in the HF + DH group (Fig. 1A).

Expression of uric acid metabolism-related genes in hyperuricemic mice

As shown in Fig. 1B, the qPCR test results showed that compared to those in the CT group, the transcription levels of ADA and XOD in the liver in the HF group were significantly upregulated (p < 0.01). In mice that received low doses of S. reiliana supplementation, the transcription levels of the XOD gene were restored to normal (p < 0.5). GLUT9, URAT1 and UMOD were significantly upregulated in the HF group (p < 0.001), whereas the expression of ABCG2 and MRP4 was significantly downregulated. Compared with those of mice in the HF group, the XOD gene transcription levels were significantly higher in the HF + DH group. GLUT9, URAT1 and UMOD were significantly upregulated in the HF + DL group and HF + DH group. ABCG2 and MRP4 were significantly upregulated in the HF + UL, HF + UH, HF + DL and HF + DH groups (p < 0.001).

Expression of inflammatory factors in hyperuricemic mice

As shown in Fig. 1C, compared with those in the CT group, the transcription levels of inflammatory factors (IL-1β and IL-6) and the anti-inflammatory factor TGF-β in the HF group were significantly increased in both the liver and kidneys (p < 0.05). Compared with those in the HF group, the
transcription levels of IL-1β, IL-6 and TGF-β in the HF + UL and HF + UH groups were significantly decreased (p < 0.05). However, there were opposite trends in the HF + DL and HF + DH groups. Similarly, compared with those in the CT group, the transcription levels of NLRP3 and Caspase-1 in the HF group were significantly increased (p < 0.05). Compared with those in the HF group, the transcription levels of NLRP3 and Caspase-1 in the HF + UL, HF + DL and HF + DH groups were significantly increased (p < 0.05) (Fig. 1C). Similarly, the transcription levels of MyD88, TRAF6 and NF-κB were significantly upregulated in the HF group compared with the CT group (p < 0.01), whereas both HF + UL and HF + UH treatment significantly downregulated the transcription of all of these genes (Fig. 1C).

Changes in the structure of the gut microbiota in hyperuricemic mice

The metagenomic sequencing results showed that a high-fructose diet can increase the diversity and abundance of the gut microbiota of mice, and the observed species index and Shannon index were highest in the HF + DL group (Table S4). Through weighted principal coordinate analysis (UniFrac PCoA) (Fig. S4), it was found that the structure of the gut microbiota of the mice in the HF + DH group was closest to that of the mice in the HF group, and the structure of the gut microbiota of the mice in the HF + AL group was closest to that of the mice in the CT group. At the phylum level (Fig. 2A), compared with that in the HF group, the relative abundance of Bacteroides in the CT group was decreased from 67.17% to 72.93%. Among them, the HF + UH group had the largest decrease; the abundance dropped from 67.17% to 34.81%. The relative abundance of Bacteroides in the HF + DH group increased from 67.17 to 72.93%. Compared with that in the HF group, the relative abundance of Proteobacteria in each group except for the HF + DL group was reduced.

As shown in Fig. 2A, at the genus level, the relative abundance of Muribaculum increased from 17.80% in the HF group to 21.08% in the HF + DH group and decreased from 17.80% in the HF group to 7.10% in the HF + UH group. The relative abundance of Prevotella was highest in the HF + DH group (17.19% and 17.36%, respectively) and lowest in the HF + UH group (7.10%). Compared with that in the model group, the maximum relative abundance of Clostridium in the HF + DL group was 9.74%, while the relative abundance in the HF + UL group decreased from 13.91% to 6.98%. As shown in Fig. 2B, further analysis in the form of a heatmap at the genus level found that in the CT group, compared with the other groups, the abundance of Acetatifactor was the highest (3.18%), and the abundance of Alistipes was low (1.93%). In the HF group, compared with the other groups, the abundance of Alistipes was the highest (3.87%), and the abundance of Roseburia was relatively low (1.62%). In the HF + Al group, the abundance of Acetatifactor was high (2.51%), and the abundance of Paramuribaculum was low (1.65%). Compared with other groups, the abundances of Ruminococcus in the HF + UL group was the highest (3.70%), and the abundance of Acetatifactor was low (1.20%). Compared with other groups, the abundances of Chlamydia, Lachnoclostridium and Anaerotruncus in the HF + UH group were higher, at 26.25%, 3.64% and 2.17%, respectively. Compared with the other groups, the abundances of Eubacterium (3.35%), Dorea (2.12%) and Helicobacter (1.06%) in the HF + DL group were higher. Compared with the other groups, the abundance of Bacteroides in the HF + DH group was the highest (16.48%), and the abundance of Oscillibacter was lower (1.63%).

The data showed that at the species level, the relative abundance of Muribaculum intestinalis was downregulated compared with that in the HF group, while it was the least downregulated in the HF + DH group, decreasing from 24.85% to 21.60%. The Bacteroides acidifaciens (BA) abundance increased from 13.16% in the HF group to 18.15% in the HF + DH group, while the relative abundance in the other groups was lower than that in the HF group. Between the CT group and the HF group, Lactobacillus murinus increased from 0.78% to 4.02%, and the relative abundance dropped to 0.52% in the HF + UL group (Fig. 2A). As shown in Fig. 2B, further analysis in the form of a heatmap at the species level found that the abundance of Lactobacillus murinus was the highest (3.79%) and the abundance of Alistipes senegalensis was lower (0.69%) in the CT group than in the other groups. In the HF group, compared with the other
As shown in Fig. 2C, the primary metabolic pathways of gut microbiota in hyperuricemic mice. A Influence on the modulation of the gut microbiota structure in hyperuricemic mice. a, Classification at the phylum level. b, Classification at the genus level. c, Classification at the species level. B Cluster analysis of gut microbiota. a, Heatmap at the genus level. b, Heatmap at the species level. C Functional analysis of the intestinal microflora in hyperuricemic mice. a, KEGG pathway classification. According to KEGG labeling, 405457 unigenes were counted, and the Mann–Whitney U test was performed. Data with FDR values <0.05 were selected for plotting. The left vertical axis is the secondary classification information for the KEGG pathway, the right vertical axis is the primary classification information for the KEGG pathway, and the horizontal axis represents the percentage of unigenes annotated. b, Analysis of KEGG pathways corresponding to the unigenes with differential abundance. Pathway annotation information for the top 30 most abundant KEGG terms in the PathwayEntry database was selected to analyze the differences between the metabolic pathways of hyperuricemia after treatment of mice with S. reilianum polysaccharides and P. dactylifera monosaccharides. c, Analysis of the different unigenes corresponding to strains and pathways.

As Fig. 2C shows, compared with those in the CT group, the abundances of unigenes related to carbohydrate metabolism (254085) and amino acid metabolism, and the abundances of unigenes related to purine metabolism, glycolysis/gluconeogenesis, fructose and mannose metabolism were increased in the HF group, but the abundances of unigenes related to the two-component system and quorum sensing were decreased in the HF group. Compared with those for the HF group, the results for the HF + AL group and the HF + UL group were exactly the opposite. The abundances of unigenes related to purine metabolism, glycolysis/gluconeogenesis, fructose and mannose metabolism, and nucleotide excision repair were decreased, while the abundances of unigenes related to the two-component system and quorum sensing were increased. These changes were more obvious in the HF + UH group than in the other groups; unigenes related to the two-component system, flagellar assembly, fructose and mannose metabolism, bacterial chemotaxis, mannose metabolism and ABC transporters were the most drastically altered. The abundance of unigenes related to purine metabolism, alanine, aspartate and glutamate metabolism, oxidative phosphorylation and pyruvate metabolism was lower in the HF + DL group than in the other groups. However, in the HF + DH group, unigenes related to the two-component system, ABC transporters, flagellar assembly, and cyanoamino acid metabolism were the least abundant.

The metabolic pathways associated with 82 differentially expressed genes and the corresponding species were screened, as shown in Fig. 2C. The species corresponding to Unigene582 was Muribaculum intestinale, and the corresponding metabolic pathway was purine metabolism. The highest abundance (in the HF group) was 16154.22, and the lowest abundance (in the HF + UH group) was 5560.64. Unigene1382 corresponded to Odoribacter splanchnicus, and the corresponding metabolic pathway was glycolysis/gluconeogenesis. The highest abundance (in the HF group) was 2392.98, while the abundance was relatively low in the HF + UH group. The corresponding species of Unigene98 was Hungatella hathewayi, and the corresponding metabolic pathway was amino sugar and nucleotide sugar metabolism. The abundance was relatively low in the HF + UH group and was highest in the HF + DH group. The corresponding species of Unigene660 and Unigene9163 were Bacteroides vulgaris and Prevotella copri, and the corresponding metabolic pathways were phenylalanine, tyrosine and tryptophan biosynthesis and cysteine and methionine metabolism. The abundance was highest in the HF group and the HF + DH group, while the content was lowest in the HF + UH group.

Serum metabolites in hyperuricemic mice

The statistics showed that 8051 and 8502 metabolites were obtained by the POS (positive) and NEG (negative) models, respectively, 4579 and 4555 of which were annotated (Table S5). PCA showed that the distribution of sample metabolites between different groups had a discrete trend,
indicating that there were differences in serum metabolites after *S. reiliana* polysaccharide and *P. dactylifera* monosaccharide intervention (Fig. 3). The results indicated that there were differences between the HF + DH group and the HF group in the POS mode and NEG mode. The difference between the HF + UL group and the CT group was the smallest. The difference between the HF + DH group and the HF + AL group was the largest.

As shown in Fig. 4 (Table S6-11), 30 differential metabolites were screened out in the CT group compared with the HF group, and acylcarnitine was upregulated. The abundance of sulfanilamide, trans-aconitic acid and linoleic acid was downregulated. The abundance of isonicotinic acid, propionic acid, trans-aconitic acid and phenyllactic acid was upregulated in the HF + AL group, while the abundance of uridine, uracil, and hippuric acid was downregulated. The secondary serum metabolites unique to the HF + AL group were phenyllactic acid, acylcarnitine, propionic acid, uracil, L-histidine and D-ornithine. In the HF + UL group, the abundances of taurodeoxycholic acid and propionic acid were upregulated, and the abundances of taurocholic acid, uridine, and kynurenic acid were downregulated. In the HF + UH group, the abundances of trans-aconitic acid, trans-caffeic acid, propionic acid, and 2-arachidonic glycerol were upregulated, while the abundances of uridine and aniline were downregulated. The abundances of isonicotinic acid, trans-aconitic acid, and niacin in the HF + DL group were upregulated, and the serum metabolites that were downregulated included uridine, acylcarnitine, taurocholate and glycocholic acid. Unique secondary serum metabolites in the HF + DL group included glycolic acid and niacin. In the HF + DH group, the abundance of trans-aconitic acid was upregulated, while the abundances of uridine, acylcarnitine, taurocholate and phenyllactic acid were downregulated.

**KEGG pathways enriched for the different serum metabolites and the related pathways associated with the differential metabolites between groups**

The metabolites identified above in the POS and NEG ion modes were assigned to primary metabolic pathways (Fig. 5A) in the KEGG database. The top priority was global and overview maps, followed by maps of lipid metabolism, amino acid metabolism, carbohydrate metabolism, and metabolism of cofactors and vitamins. The top 20 KEGG pathways of the determined serum metabolites under POS and NEG ion modes are shown in Fig. 5A. The serum metabolites were most enriched in metabolic pathways, followed by protein digestion and absorption, glycerophospholipid metabolism, and biosynthesis of amino acids.

Pathway analysis of patient biomarkers was performed using metaX, and the results and pathways are shown in Fig. 5B. The enriched pathways of the differential metabolites in the HF group compared with the CT group (Fig. 5B) mainly included linoleic acid metabolism, arachidonic acid metabolism and biosynthesis of unsaturated fatty acids. The differential metabolites in the HF + AL group compared with the HF group (Fig. 5B) were enriched in phenylalanine metabolism; alanine, aspartate and glutamate metabolism; pyrimidine metabolism, etc. In the HF + UL group (Fig. 5B), the differential metabolites were enriched in the biosynthesis of phenylpropanoids, phenylalanine metabolism and pyrimidine metabolism. The serum metabolites in the HF + UH group were mainly enriched in phenylpropanoid biosynthesis and pyrimidine metabolism (Fig. 5B). In

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**Fig. 3** PCA of the serum metabolite ions in hyperuricemic mice. Each point in the figure represents a sample, and the similarities and differences among all samples are reflected in the separation and aggregation trends of the points in the figure. The clustering of points indicates that the observed variables have a high degree of similarity, and the dispersion of points indicates that the observed variables have obvious differences. **a** PCA in POS mode, **b** PCA in NEG mode.
the HF + DL group (Fig. 5B), the main enriched pathways were bile acid biosynthesis, biosynthesis of phenylpropanoids and secondary bile acid biosynthesis. Serum metabolites in the HF + DH group were enriched in secondary bile acid biosynthesis, taurine and hypotaurine metabolism and sphingolipid metabolism pathways (Fig. 5B).

Discussion

Previous studies have shown that fructose generates uric acid during its metabolism and that serum urate (Le et al. 2012) and urinary uric acid increase acutely following fructose ingestion. Continuous intake of high fructose is closely related to the occurrence and development of hyperuricemia (Wang et al. 2016). Our study demonstrated that feeding mice a 13% (w/v) fructose solution established a stable hyperuricemia animal model with pathological characteristics similar to those of human hyperuricemia. Treatment with S. reiliana polysaccharides significantly reduced serum uric acid levels in hyperuricemia mice. It is recognized that increased uric acid causes damage to liver and kidney functions. Metabolism of fructose increases the burden on the liver (Muriel et al. 2021). Uric acid can be ionized into urate, and the kidneys are the main sites of urate deposition. The results also showed that the serum creatinine and urea nitrogen levels in the model group were significantly higher than those in healthy mice, and the serum creatinine and urea nitrogen levels were decreased after S. reiliana polysaccharide treatment. These may be some of the effects by which S. reiliana polysaccharides alleviate hyperuricemia, while P. dactylifera monosaccharides exerted the opposite
Fig. 5 Effects on serum metabolite-related pathways in hyperuricemic mice. A. Analysis of the metabolic pathways associated with the serum metabolites of hyperuricemic mice. a. Total serum metabolites in the POS model. b. Total serum metabolites in the NEG model. The first-level KEGG pathway terms are displayed and distinguished by different colors. The second-level KEGG pathway terms are on the abscissa, and the numbers of metabolites are on the ordinate. The identified metabolites were classified into the top 20 KEGG pathways. c. POS model. d. NEG model. The x-axis represents the top 20 KEGG pathways, and the y-axis represents the number of identified metabolites involved in these pathways. B. Different pathways related to serum metabolites in each group compared with the HF group. a. Pathway diagram of differential metabolite enrichment in the HF and CT groups. b. Pathway diagram of differential metabolite enrichment in the HF + AL and HF groups. c. Pathway diagram of differential metabolite enrichment in the HF + UL and HF groups. d. Pathway diagram of differential metabolite enrichment in the HF + UH and HF groups. e. Pathway diagram of differential metabolite enrichment in the HF + DL and HF groups. f. Pathway diagram of differential metabolite enrichment in the HF + DH and HF groups.
effects. Several enzymes, including ADA and XOD, are key enzymes of purine nucleotide catabolism and play an important role in the production of uric acid in the liver (Zhu et al. 2021). The kidneys then rely on uric acid transporters to excrete uric acid. Uric acid transporters can be divided into two categories: uric acid-reabsorbing proteins (GLUT9, URAT1 and UMOD) and uric acid-secreting proteins (ABCG2 and MRP4) (Wan et al. 2019). In this study, the results suggested that *S. reiliana* polysaccharides inhibited ADA expression and promoted ABCG2 and MRP4 expression, thereby inhibiting uric acid biosynthesis and promoting excretory pathways. *P. dactylifera* monosaccharides promoted XOD expression and increased uric acid synthesis, which may have been the cause of the aggravation of uric acid accumulation.

An inflammatory response is a characteristic pathological feature of hyperuricemia (Zhai et al. 2015). Fructose-1-phosphate is the first product of fructose metabolism. It is easily metabolized and transformed into glycerol triphosphate or long-chain fatty acids; triacylglycerol is then synthesized and accumulates in the liver, which promotes fatty liver, thus burdening the liver. Studies have shown that hyperuricemia can also induce kidney disease (Ma et al. 2021). Kidney injury can lead to reduced clearance rates of creatinine and urea nitrogen, can increase the serum creatinine and blood urea nitrogen contents, and can promote the expression of proinflammatory cytokines and chemokines (Zhou et al. 2012). Inflammatory factors (IL-1β, IL-6, and TNF-α) are closely related to the TLR4/MyD88/NF-κB signaling pathway and the NLRP3 inflammasome (Tan et al. 2019). In this study, *S. reiliana* polysaccharide dietary intervention not only inhibited the activation of the NLRP3 inflammasome complex and blocked the TLR4/MyD88/NF-κB signaling pathway but also downregulated the transcription of the proinflammatory cytokines IL-1β and IL-6 and upregulated the transcription of the anti-inflammatory cytokine TGF-β, thereby reducing liver and kidney inflammation.

In addition to the kidneys, the intestine is also one of the important organs involved in the excretion of uric acid, and one-third of uric acid is excreted through the intestine. Dysregulation of the gut microbiota can affect uric acid metabolism and lead to elevated serum uric acid levels. Therefore, dietary control of the gut microbiota may be a potential target for alleviating hyperuricemia (Zhang et al. 2020). Metagenomic detection of gene function is a good strategy with which to explore the interaction between the gut microbiota and the host. In terms of the species composition of the gut microbiota, we found that the gut microbiota structure of mice treated with allopurinol and *S. reiliana* polysaccharides was closer to that of healthy mice, while the structure of the gut microbiota of mice treated with *P. dactylifera* monosaccharides was closer to that of hyperuricemia mice. Compared with healthy mice, at the phylum level, hyperuricemia mice exhibited increased abundances of Bacteroidetes and Proteobacteria but a reduced abundance of Firmicutes, which is consistent with literature reports (Yu et al. 2018). An increased Proteobacteria abundance can be regarded as a microbial marker of gut microbiota imbalance. Cardiovascular disease complications were found to be associated with Proteobacteria levels in the blood, consistent with an increased incidence of hyperuricemia. The abundances of Proteobacteria and Bacteroidetes decreased most after treatment with *S. reiliana* polysaccharides. The increase in the Bacteroidetes proportion will likely enhance the uptake of monosaccharides in the host intestinal tract and promote the synthesis of triacylglycerol in the liver, leading to insulin resistance (Ahmad et al. 2019). Yu et al. (Yu et al. 2018) found in an experiment that the abundances of several bacteria with purine absorption and uric acid decomposition functions, such as *Lactobacillus* and *Clostridium*, were decreased, which is consistent with our experimental results. However, the levels of *Muribaculum*, *Prevotella* and *Muribaculum intestinale* were increased among the intestinal microbes of mice treated with *S. reiliana* polysaccharides.

*Muribaculum intestinale*, BA and *Odoribacter splanchnicus* were enriched in the intestines of high fructose-treated mice. The abundance of *Muribaculum intestinale* was elevated in mice treated with *P. dactylifera* monosaccharides. The corresponding metabolic pathway of *Muribaculum intestinale* was purine metabolism, which is related to amino acid metabolism. Uric acid is an important metabolite of purine metabolism. The metabolic pathway of *Odoribacter splanchnicus* was glycolysis/glucogenesis. The abundance was highest in the hyperuricemic mice, followed by the mice treated with *P. dactylifera* monosaccharides, and the abundance was lowest in mice treated with *S. reiliana* polysaccharides and healthy mice. In this study, uric acid levels were significantly reduced in mice treated with *S. reiliana* polysaccharides, suggesting that dietary intervention may alleviate hyperuricemia in mice by regulating purine metabolism. BA can degrade mucin, the protective layer of the colon, and increase the production of the short-chain fatty acids acetic acid and succinic acid (Randhawa et al. 2014). Both *Muribaculum intestinale* and BA cause associated inflammation of the gut. *Lactobacillus rhamnosus* can repair intestinal inflammation and has anti-inflammatory effects; however, the abundance of *Lactobacillus rhamnosus* was the lowest in the hyperuricemic mice. Gut microbiota functional analysis showed that the abundances of purine metabolism- and glycolysis/glucogenesis-related microbes were increased in high uric acid mice and *S. reiliana* monosaccharide-treated mice and were decreased in allopurinol- and *P. dactylifera* polysaccharide-treated mice.
The findings indicate that the consumption of *S. reiliana* can relieve uric acid imbalance and that the gut microbiota affects the human body by causing major changes in host metabolism or substrate cometabolism.

Metabolomics mainly involves the study of the dynamic changes in all metabolites in the host body under conditions of disease or exogenous substance exposure to reflect pathophysiological changes and to reveal pathogenesis. Analysis of the changes in serum metabolism in the mice on a high-fructose diet revealed that similar to previous research results, the main metabolites with differences in serum were arachidonic acid, hippuric acid, uridine, uracil, kynurenic acid, etc. (Liu et al. 2011). These differential metabolites are mainly involved in glucose metabolism, the TCA cycle, tryptophan metabolism, purine metabolism, lipid metabolism, amino acid metabolism, etc. (Wang et al. 2016). After *P. dactylifera* monosaccharide treatment, the levels of bile acid metabolism, tryptophan metabolism and purine metabolism were elevated, indicating that a high-fructose intake is related to metabolic disorders in mice. Abnormal bile acid metabolism and levels are associated with metabolic disorders such as liver injury, diabetes, obesity, cardiovascular diseases, digestive system diseases (inflammatory bowel disease, colorectal cancer, etc.) and kidney disease (Gai et al. 2016). It has been reported that hyperuricemia may affect tryptophan metabolism (Perez-Pozo et al. 2010), purine metabolism, the purine nucleotide cycle and amino acid metabolism, and uric acid is an important metabolite of purine metabolism (Liao et al. 2019). Studies have shown that kynurenic acid, an important metabolite of the tryptophan pathway, is elevated in rats with renal insufficiency. In addition, the serum of mice treated with a high-fructose diet and *P. dactylifera* monosaccharides also included markers associated with kidney injury, including uridine in the nucleotide metabolic pathway. Hippuric acid was used as a biomarker of bacterial imbalance and abnormal metabolism of the microflora (Calvani et al. 2010). Arachidonic acid is the precursor of leukotirole biosynthesis in the body and is related to many inflammatory conditions, including gout (He et al. 2012). The expression of arachidonic acid and linoleic acid was decreased significantly in hyperuricemic mice, while it was increased after low-dose *S. reiliana* treatment. The tricarboxylic acid cycle is an important part of energy metabolism and a pathway for the oxidation of energy substances such as sugars, fatty acids and amino acids. The levels of propionic acid, succinic acid and citric acid were decreased, suggesting abnormal energy metabolism in hyperuricemic mice after *P. dactylifera* monosaccharide treatment.

We further explored the correlations among different flora, serum metabolites and metabolic pathways and found that a high-fructose diet resulted in metabolic disorders of succinic acid, hippuric acid and L-aspartate cytidine in mice, in which carbohydrate metabolism and lipid metabolism were most involved. For example, both *Bacteroides thetaiotaomicron* and succinic acid were enriched in the TCA cycle. *B. thetaiotaomicron* and maleic acid were enriched in the butanoate metabolism pathway. *Anaerosporobacter mobilis* and uridine were enriched in the pyrimidine metabolism pathway. These results indicated that *S. reiliana* could alleviate fructose-induced hyperuricemia from physiological and biochemical points of view. Dietary intervention changed the intestinal flora and serum metabolites of mice, thus reducing the uric acid content of the body and relieving hyperuricemia. After eating, pyruvate metabolism and the tricarboxylic acid cycle are both in a state of decline. Pyruvate is the final product of the glycolysis pathway and is converted into lactic acid in the cytoplasm or enters the mitochondria for oxidation to produce acetyl coenzyme A, which enters the TCA cycle, thereby inhibiting the TCA cycle. This phenomenon presumably occurs because umami polysaccharides inhibit the unrestricted metabolism of fructose in the liver.

**Conclusion**

Polysaccharides are polymerized from monosaccharides, but their activities are very different. Most of the previous studies were focused on the activity of polysaccharides, and few monosaccharides and polysaccharides were combined for joint analysis. This study shows that *S. reiliana* polysaccharides and *P. dactylifera* monosaccharides have effects on hyperuricemia. *S. reiliana* polysaccharides can alleviate hyperuricemia caused by fructose to a certain extent, and excessive intake of *P. dactylifera* monosaccharides can aggravate the occurrence of high uric acid. From the perspective of the gut microbiota and serum metabolism, intake of *S. reiliana* polysaccharides improves the gut microbiota structure and metabolite profile, while *P. dactylifera* monosaccharides exert the opposite effects. Our findings help to elucidate the roles of *S. reiliana* polysaccharides and *P. dactylifera* monosaccharides in hyperuricemia, which could provide some new ideas for future research.

**Author contributions**  All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by ZW, ZZ and CL. The first draft of the manuscript was written by ZW, IH, XS and JZ and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflict of interest The authors declare no competing financial interest.

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