Supplementary information

Supplementary Table S1. Composition of the experimental diets (%, w/w)

Ingredients	Control	EtOH	EtOH+L-RR	EtOH+M-RR	EtOH+H-RR
AIN93M diet	100	100	98	96	92
Red raspberry	-	-	2	4	8
Total	100	100	100	100	100

Supplementary Table S2. Estimated values of various nutrients of AIN93M standard feed

Ingredients	**AIN93M**
Energy	3601 Kcal/kg
Total calculated digestible energy from protein	14.1%
Total calculated digestible energy from lipids	10%
Water content	6.8%
Fat	4%
Carbohydrates	72.7%
Protein	12.5%
Ash	3.89%
Amino acid content	
Alanine	3.3g
Arginine	4.5g
Aspartic acid	8g
Glutamate	25.5g
Glycine	2.3g
Lysine	9.2g
Methionine	3.3g
Cystine	2.4g
Tryptophan	1.6g

Proline	14.3g
Serine	6.7g
Histidine	3.3g
Leucine	10.9g
Isoleucine	5.9g
Phenylalanine	6.2g
Tyrosine	6.6g
Threonine	4.7g
Valine	7g
Mineral content	
Calcium	5000ppm
Phosphorus	3000ppm
Potassium	3600ppm
Sodium	1033ppm
Magnesium	511ppm
Iron	45ppm
Zinc	35ppm
Copper	6ppm
Iodine	0.2ppm
Chromium	1ppm
Inorganic Sulfur	300ppm
Chlorine	1613ppm
Vitamin content	
Vitamin A	4IU/g
Vitamin D	1IU/g
Vitamin E	0.075IU/g
Vitamin K	0.86 ppm
Thiamine, B1	5 ppm
Riboflavin	6 ppm
Niacin	30 ppm
Pantothenic acid	15 ppm
Vitamin B6	6 ppm
Choline	1000 ppm
Folic acid	2ppm
Biotin	0.2ppm
Vitamin B12	25ppb

Product code: LAD3001M.

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Method for the determination of red raspberry polyphenols composition

Red raspberry extract was analyzed by high-performance liquid chromatography (HPLC) based on targeted and untargeted method. The analytical conditions were as follows: HPLC column, shim-pack GISS C18 (pore size 1.9 μm, length 2.1 × 100 mm); the solvent system was solvent A (aqueous 0.04% acetic acid) and solvent B (acetonitrile (0.04% acetic acid)). The gradient program was 0 min, 5% B; 12.0 min, 95% B; 13.2 min, 95% B; 13.3 min, 5% B; 15.0 min, 5% B, with a flow rate of 0.4 mL/min. The temperature was 40 ℃ and the injection volume was 2 μL. Raspberry extract was performed in the Full-Scan mode by Q Exactive Focus Orbitrap LC-MS/MS (Thermo Scientific, USA) Using Compound Discoverer 3.3 software to analyze the raw data. The ESI source operation parameters were as follows: nebulizing gas flow, 3 L/min; heating gas flow, 10 L/min; interface temperature, 500 ℃; DL temperature, 250 °C; heat block temperature, 400 °C; drying gas flow, 10 L/min.

Identification of compounds

The identification was carried out by comparison of the accurate m/z values, the retention time (RT), and the fragmentation patterns with those obtained from available standards analyzed in the same conditions. For high-quality (S/N>10) metabolic signals, we compared the MS2 spectral information of metabolic signals with the database by using Compound Discover 3.3 software and annotated these metabolic signals in batches. Then we identified metabolic signals that did not match the information in the database by querying the MS2 spectral data taken from the literature or to search the databases (e.g., METLIN, MassBank).

Supplementary Table S3. Primers used in this study

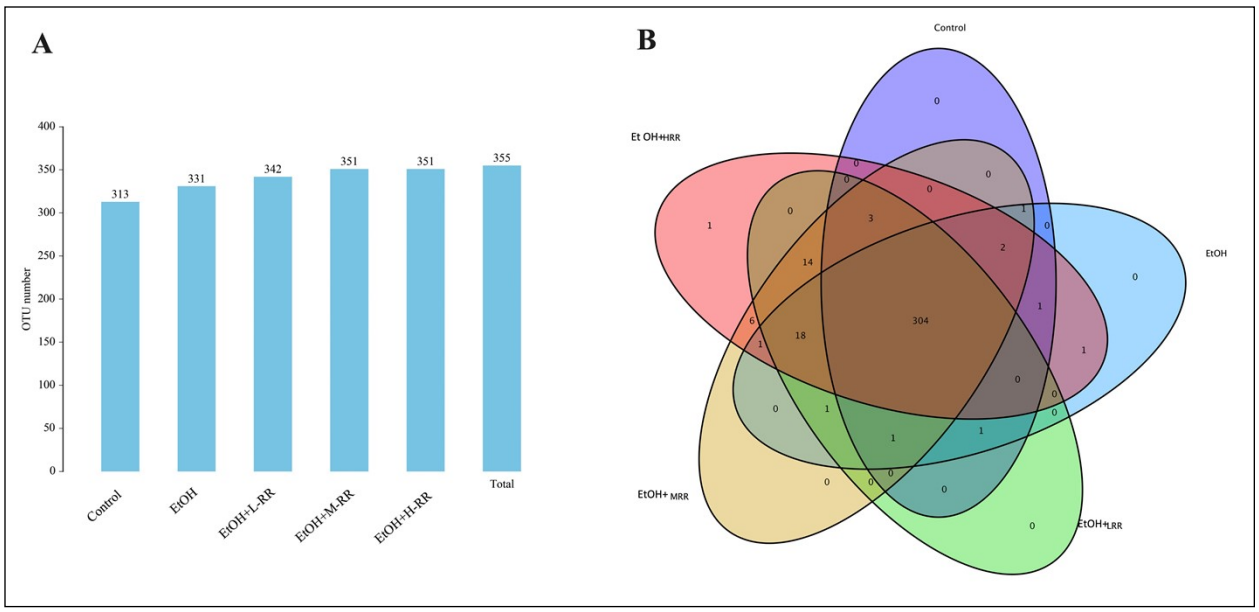
Gene name	Primer sequence	Gene ID/Reference
ZO-1	F: CGGAACTATGACCATCGCCTAC R: CTTCGGGATGTTGTCTGGAGTC	NM-001163574.1
Occludin	F: TTCCACACTTGCTTGGGACAGA R: TCCGCCATAGCCATAGCCATAG	NM-0088756.2
Claudin-1	F: GGGCTGATCGCAATCTTTGTGT R: CCACTAATGTCGCCAGACCTGA	NM-016674.4
Claudin-4	F: GGCTGAGCGATGGCGTCTAT R: CGATGTTGCTGCCGATGAAGG	NM-009903.2
E-cadherin	F: GCCATCGCCTACACCATCGT R: GCAGCCTGAACCACCAGAGT	NM-009864.3
CD14	F: GAGCGTGTGCTTGGCTTGTT R: CCGTAAGCCGCTTTAAGGACA	[1]
TLR4	F: GCATGGATCAGAAACTCAGCAAA R: CTCCACAGCCACCAGATTCTC	[1]
NF-κB	F: GCTGCCAAAGAAGGACACGACA R: GGCAGGCTATTGCTCATCACAG	NM_008689
CYP 2E1	F: TGGGGAAACAGGGTAATGAG R: CTGGCCTTTGGTCTTTTTGA	[2]
β-actin	F: GGCTGTATTCCCTCCATCG R: CCAGTTGGTAACAATGCCATG	NM_007393.5

F, forward; R, reverse

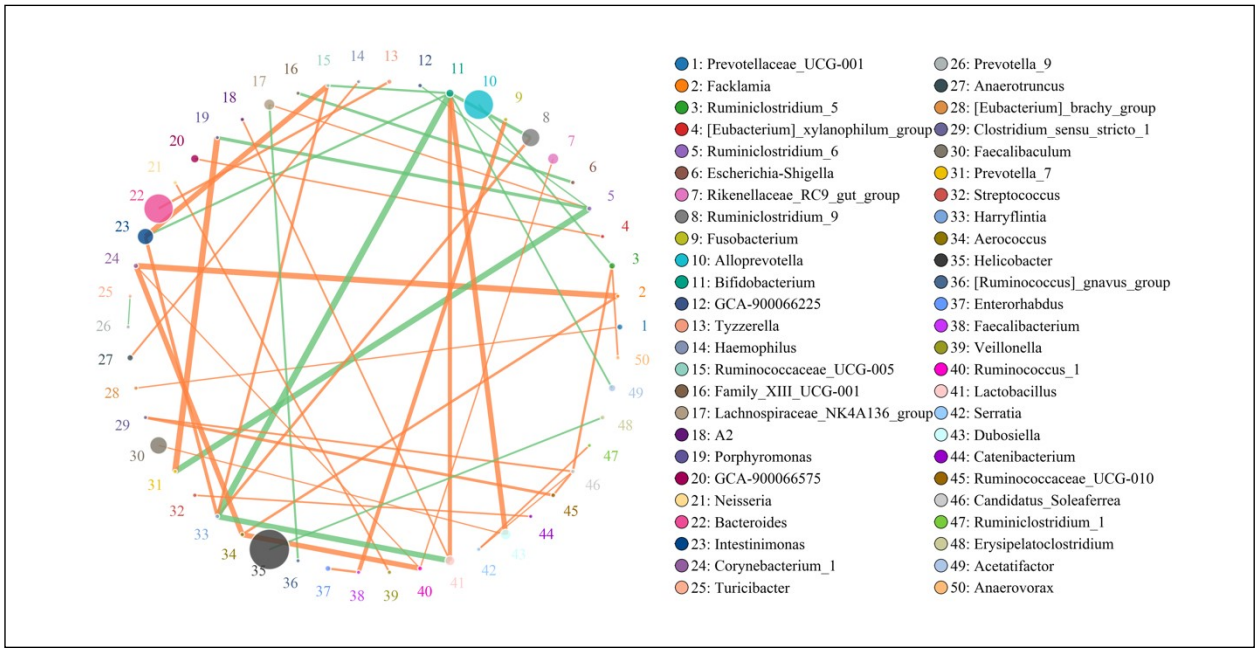
Primers were designed using BLAST of NCBI (USA) and synthesized by TSINGKE Biotech Co., Ltd. (Wuhan, China).

Supplementary Table S4. Antibodies and their dilution ratio used in this study

Detection antibody	Company	Item No.	Dilution with TBST
Mouse monoclonal antibody β-actin (42KD)	Wuhan Boster Biological Engineering Co., Ltd.	BM0627	1:500
Rabbit anti ZO-1 (240KD)	Boster	PB9234	1:1000
Rabbit anti Occludin (59KD)	Affinity	DF7504	1:2000
Mouse anti E-cadherin (120KD)	Wuhan Sanying Biotechnology Co., Ltd.	60335-1-Ig	1:3000
Rabbit anti Claudin1(23KD)	Affiniy	AF0127	1:2000
Rabbit anti Claudin4 (22KD)	Wuhan Sanying Biotechnology Co., Ltd.	16195-1-AP	1:1000
Rabbit anti MLC2 (19KD)	Wuhan Sanying Biotechnology Co., Ltd.	10906-1-AP	1:2000
Mouse anti p-MLC2 (18KD)	CST	3675S	1:1000
Rabbit anti MLCK (211KD)	Affinity	AF5314	1:1000
Rabbit anti NFKB (65KD)	Invitrogen	PA5-17264	1:1000
Rabbit anti p-NFKB (60KD)	Affinity	AF2006	1:1000
HRP-labeled goat anti-mouse secondary antibody	Boster	BA1051	1:10000
HRP-labeled goat anti-rabbit secondary antibody	Boster	BA1054	1:10000



Supplementary Fig. 1. (A) Operational taxonomic unit (OTU) number in cecal samples of mice in the five groups after six weeks of treatment. (B) Venn diagram showing microbial common and unique features among mice from the five experimental groups.



Supplementary Fig. 2. Cecal content species network at genus level of mice in the five experimental groups.

Circles represent species and the size of the circle corresponds to the abundance; The correlation between two species is represented by the edges, the thickness of the edge represents the strength of the correlation, and the color of the line: orange represents the positive correlation, while green represents green the negative correlation.

References:

1 J. Xiao, R. Zhang, Y. Wu, C. Wu, X. Jia, L. Dong, L. Liu, Y. Chen, Y. Bai and M. Zhang, Rice Bran Phenolic Extract Protects against Alcoholic Liver Injury in Mice by Alleviating Intestinal Microbiota Dysbiosis, Barrier Dysfunction, and Liver Inflammation Mediated by the Endotoxin-TLR4-NF-κB Pathway, *J. Agric. Food Chem.*, 2020, **68**, 1237–1247.

2 Y. Ren, Y. Ding, F. Meng, L. Jiang, H. Li, J. Huang, P. Yu and Z. Qiu, Quantification of CYP2E1 in rat liver by UPLC-MS/MS-based targeted proteomics assay: a novel approach for enzyme activity assessment, *Anal. Bioanal. Chem.*, 2020, **412**, 5409–5418.