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Integrative Gut Microbiota and Serum Metabolomics Reveal the Intervention Effect of Quercetin on Type 2 Diabetes

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ABSTRACT: This study aimed to investigate how quercetin alleviates type 2 diabetes mellitus (T2DM) symptoms in diet-induced T2DM rats by regulating gut microbiota and serum metabolomics. Male Sprague-Dawley rats were divided into four groups: Control, Diabetes, Diabetes + Quercetin, and Control + Quercetin. After 18 weeks of intervention, biochemical parameters, liver histopathology, gut microbiota, and serum metabolomics were analyzed. Results showed quercetin reduced fasting blood glucose, improved lipid profiles and alleviated liver damage in DM rats. It also reversed T2DM-induced decreases in gut microbiota diversity and modulated microbial composition. Metabolomics revealed quercetin decreased SM(d18:1/24:1) and enriched pathways like sphingolipid metabolism. Integrated analysis linked microbiota to metabolites and biochemical parameters. *g_Alistipes* was negatively correlated with FBG and SM(d18:1/24:1). In conclusion, quercetin exerts distinct anti-diabetic effects in diet-induced T2DM rats by remodeling gut microbiota composition and regulating serum metabolomic profiles. Furthermore, deciphering the crosstalk between quercetin-modulated gut microbial taxa and key metabolic pathways deepens our understanding of the microbiota-metabolite axis in mediating diabetic phenotypes.

Keywords: Quercetin; Phytochemicals; Type 2 Diabetes Mellitus; Serum Metabolomics

1. Introduction

Type 2 diabetes mellitus (T2DM) is a prevalent metabolic and endocrinological disorder. The NCD Risk Factor Collaboration estimated that 828 million adults worldwide had T2DM in 2022^[1]. The development of T2DM results from various mechanisms, including β -cell dedifferentiation, oxidative stress, or inflammation^[2]. The molecular pathogenesis of T2DM is not yet fully understood. Recent studies have indicated that the occurrence and development of T2DM are also related to gut microbiota^[3]. A cross-sectional study based on the National Health and Nutrition Examination Survey from 2007-2018 found an inverse association between gut microbiota diversity and T2DM and insulin resistance^[4]. Meta-Analysis have found that reducing

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microbial dysbiosis helps improve insulin resistance and glucose metabolism^[5]. The gut microbiome presents a potential target for the prevention and management of T2DM, and further research is needed to definitively establish its role.

Polyphenols are promising candidates for T2DM control, primarily due to the side effects of standard blood sugar-lowering medications^[6]. Quercetin, a common polyphenol found abundantly in fruits and vegetables, is an important flavonoid with prominent bioactivities relevant to T2DM, such as hypoglycemic, hypolipidemic, anti-inflammatory, and antioxidant effects^[7-9]. A cross-sectional study involving approximately 16,000 Chinese individuals indicated an inverse relationship between quercetin intake and T2DM prevalence^[10]. Notably, quercetin can alter gut microbiota diversity and the abundance of specific microorganisms^[11]. Quercetin can reshape gut microbiota to modulate metabolism, thereby exerting antidepressant and anti-obesity effects^[12, 13].

Emerging evidence supports quercetin's potential to reshape gut microbial communities in diabetic contexts, yet its integrated regulatory role in the gut microbiota-metabolite axis in diet-induced T2DM remains insufficiently explored. Our earlier research has revealed that quercetin can modulate serum metabolomics, such as glycerophospholipid metabolism, to ameliorate cardiac dysfunction and myocardial fibrosis associated with diabetic cardiomyopathy^[14]. A comprehensive multi-omics approach can facilitate the decipherment of the coordinated regulatory network underlying quercetin's anti-diabetic activity and help illuminate the synergistic mechanisms linking its effects on gut microbiota and metabolism. In the present study, we aimed to investigate the effect of quercetin on diabetes in high-fat high-sugar (HFHS) diet-induced T2DM rats, with a particular focus on gut microbiota and serum metabolomics.

2. Materials and methods

2.1 Experimental animals and treatments

Male Sprague-Dawley (SD) rats aged 8 weeks were purchased from Beijing Huafukang Biotechnology Co., Ltd. All animal experimental protocols were approved by the Ethics Committee of Laboratory Animal Welfare of the National Institute for Nutrition and Health, the Chinese Center for Disease Control and Prevention. The animals were randomly divided into four groups ($n = 12$ per group): Control group (Ct); Diabetes group (DM); Diabetes + Quercetin group (DM + Q); and Control + Quercetin group (Ct + Q).

The Ct and Ct+Q groups were fed the standard AIN-93G synthetic diet (containing 7% soybean oil and 10% sucrose), while the DM and DM+Q was fed a high-fat and high-sucrose diet (containing 10% lard, 4% soybean oil, 20% sucrose, 1% cholesterol, and 0.2% bile salts). All rats had free access to food, and the feeding period lasted 18 weeks. Additionally, the Ct+Q and DM+Q groups were supplemented with quercetin (100 mg/kg·bw) during 18 weeks^[14]. The diets were purchased from Mediciene (Yangzhou, China), and quercetin was supplied by Sigma-Aldrich (USA). Rats with a fasting blood glucose (FBG) level above 6.7 mmol/L were considered to have successful T2DM induction and were kept in the study^[15, 16].

After the intervention, the rats were anesthetized with 2% sodium pentobarbital at a weight-based dose. Blood samples were collected from the abdominal aorta prior to euthanasia, followed by dissection and storage of the liver, right kidney, and perirenal tissues for subsequent analyses.

2.2 Histopathological analysis

The liver was excised, weighed, and fixed in 4% formalin solution. Subsequently, hepatic samples were embedded in paraffin and sectioned at 5 μ m using a microtome. To analyze the general architecture of the hepatic tissue, hematoxylin-eosin (H&E) staining was performed.

2.3 Transmission electron microscope (TEM)

Another smaller fresh liver fragment (1-mm cube) was sequentially fixed with 2.5% glutaraldehyde and 1% osmium tetroxide in a pH 7.4 phosphate buffer. Following dehydration, the sample was embedded in resin, and ultrathin sections were stained with uranyl acetate and lead citrate for examination of ultrastructure by TEM.

2.4 Detection of biochemical parameters in serum

The levels of FBG were determined using the glucose oxidase method. The levels of glycated hemoglobin (HbA1c) were measured using a glycosylated hemoglobin analyzer. The levels of total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL), low density lipoprotein (LDL), serum creatinine (SCr), blood urea nitrogen (BUN), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) in serum were detected using an automatic biochemical analyzer.

2.5 Gut microbiota analysis

Total microbial genomic DNA was extracted from 4 groups of samples using the PF Mag-Bind Stool DNA Kit (Omega Bio-tek, Georgia, United States). Qualified DNA samples were applied to amplify the 16S rDNA V3-V4 region using the universal primers 338F and 806R. Further details on the polymerase chain reaction (PCR), sequencing, and data analysis are provided in the Supplementary Materials.

2.6 Serum metabolomic analysis

The details of sample preparation, along with information on sample processing, instrument parameter settings, and data acquisition and analysis, were provided in the Supplementary Materials. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis were performed on a ThermoFisher Scientific Q Exactive™ system equipped with an ACQUITYHSS T3 column (100 mm 2.1 mm i.d., 1.8 μ m; Waters, USA).

2.7 Statistical analysis

All data were presented as mean $\pm$ standard deviation (SD). R 4.4.2 software was used for statistical analysis. Origin 2024 was used to generate corresponding graphics. One-way analysis of variance (ANOVA)

was utilized to compare multiple data groups, and the least significant difference (LSD) method was employed for post hoc multiple comparisons. A P -value of less than 0.05 was considered statistically significant.

3. Result

3.1 Effects of quercetin on body weight and liver damage in DM rats

Compared to the Ct group, the liver weight and kidney weight in the DM rats were increased to (36.42 ± 3.87) g ($P < 0.001$) and (1.99 ± 0.19) g ($P = 0.005$), respectively. Quercetin did not affect the liver weight and the kidney weight (Fig.1).

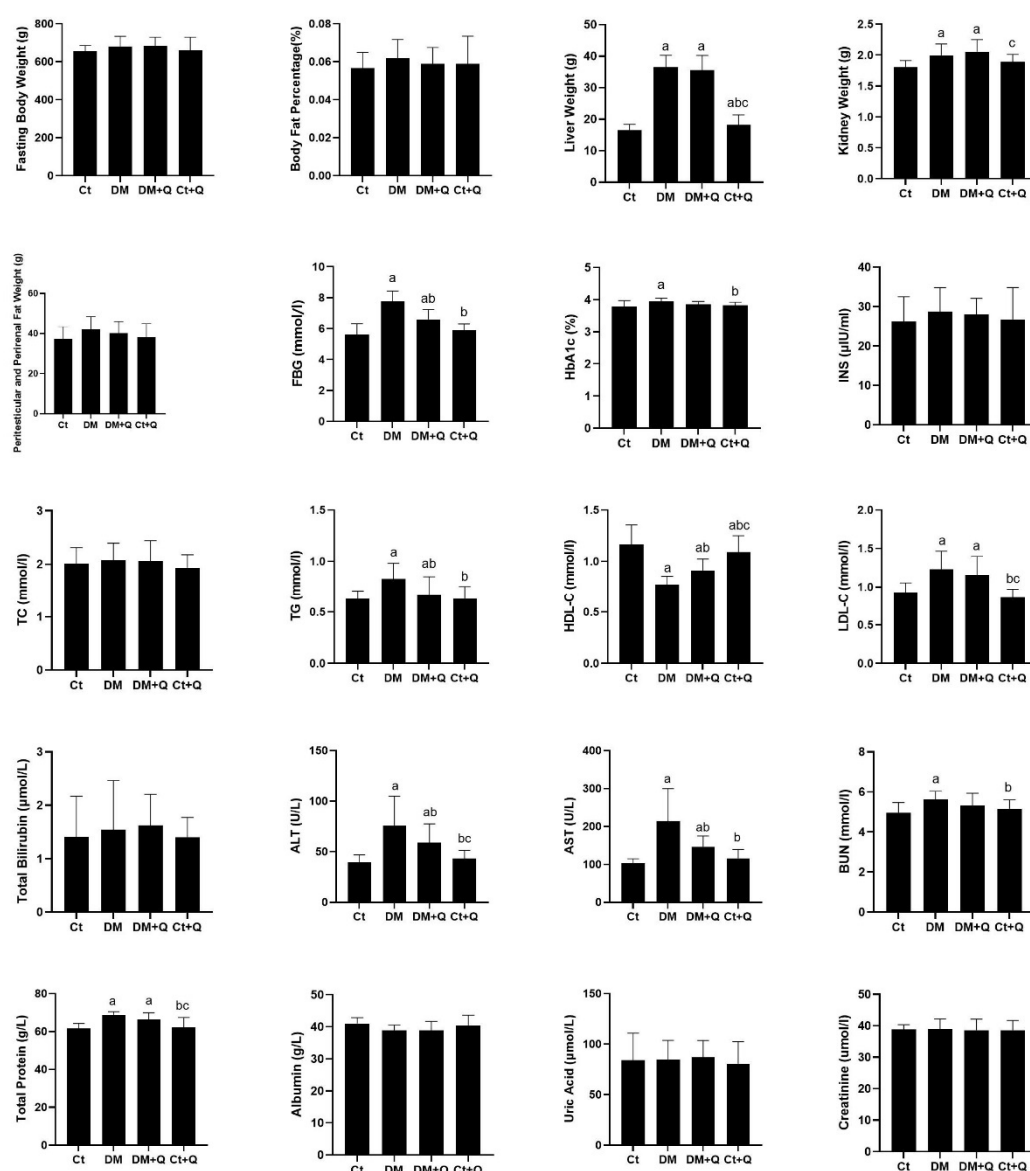


Fig.1 Effects of quercetin on the biochemical indicators of DM rats. (a. compared with the Ct control group, $P < 0.05$; b. compared with the DM control group, $P < 0.05$; c. compared with the DM+Q control group, $P < 0.05$).

As depicted in Fig.1, serum levels of FBG and HbA1c in DM rats were higher than those in Ct ($P < 0.001$; $P = 0.002$), while quercetin significantly decreased the levels of FBG in the DM rats ($P < 0.001$). The serum lipid indexes of each group were analyzed, and the results are shown in Fig.1. Compared with the Ct group, DM rats had significantly higher TG and LDL-C levels and significantly lower HDL-C levels.

Furthermore, quercetin significantly reversed the changes in TG and HDL-C ($P < 0.05$). Fig.1 shows the ALT and AST levels of the experimental animals, respectively. The ALT and AST levels of DM rats were significantly higher than those of the Ct group. After quercetin intervention, ALT and AST levels were significantly lower in the DM+Q rats than in the DM rats ($P < 0.05$).

As shown in Fig.2, H&E staining indicated that DM rats had obvious hepatic tissue disorganization compared to the Ct group. The ultrastructure of liver tissue observed by electron microscopy revealed that the mitochondria were swollen and loose, and the endoplasmic reticulum was also swollen in the DM rats. Quercetin improved these disorganizations (Fig.2).

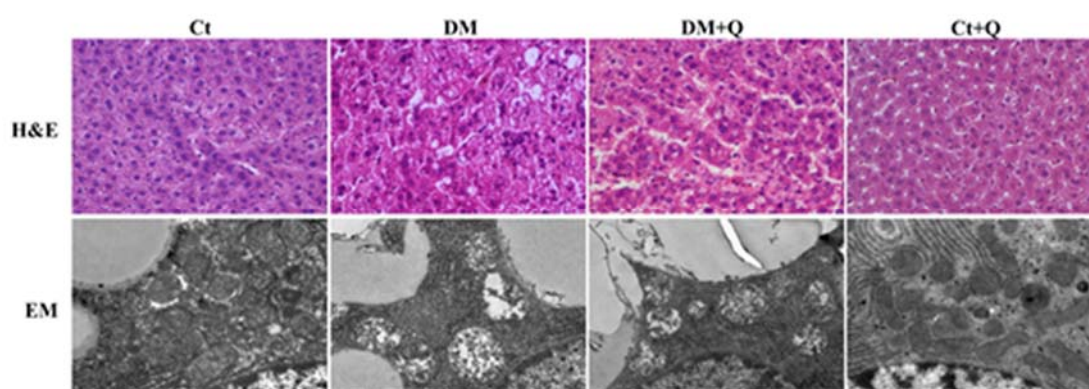


Fig.2 H&E staining (top) and transmission electron microscope (bottom) images showing the effects of quercetin on the livers of DM rats.

3.2 Quercetin reversal shifts the microbial flora in DM rats

3.2.1 Diversity analysis

Principal Component Analysis (PCA) and Principal Coordinate Analysis (PCoA) analyses are non-parametric dimensionality reduction methods. In contrast, Non-metric Multidimensional Scaling (NMDS) analysis can reflect the species information contained within the sample, represented as points in multidimensional space. As shown in Fig.3, the gut microbiota community of the DM group was significantly different from that of the Ct group. Still, intervention with quercetin changed this to some degree.

According to the α index (Fig.3), the Shannon index, the Simpson index, the Sobs index, the Richness index, the Chao1 index and the the abundance-based coverage estimator (Ace) index of the DM group were significantly lower than those of the Ct group, indicating that the richness and diversity of microorganisms were reduced under DM conditions. Quercetin intervention effectively reversed the Chao1 index and the Ace index ($P < 0.05$).

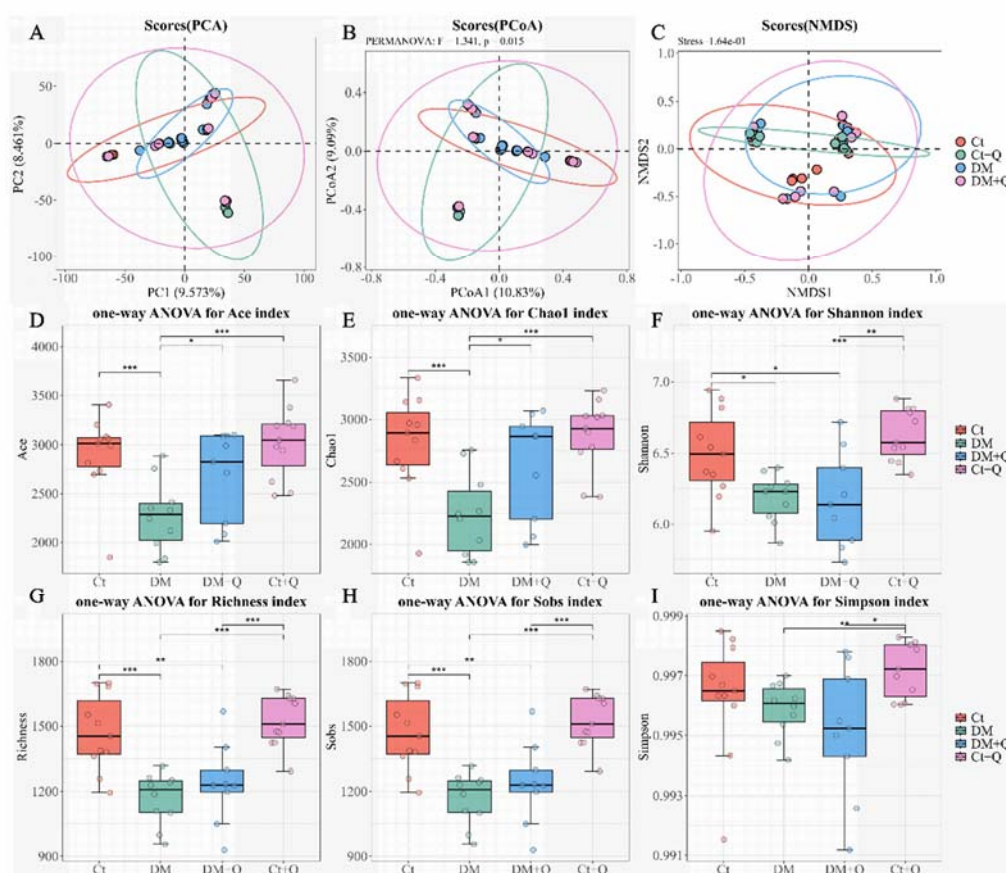


Fig. 3 Diversity analysis of gut microbiota in DM rats. (A) PCA analysis. (B) PCoA analysis. (C) NMDS analysis. (D) Ace index. (E) Chao1 index. (F) Shannon index. (G) Richness analysis. (H) Sobs analysis. (I) Simpson analysis. (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$).

3.2.2 Gut microbiota community analysis

The microbial composition of the four groups of rats was analyzed at the phylum level. According to the Bar map of community composition in Fig.4, the dominant phyla in the four groups were *p_Firmicutes*, *p_Bacteroidota* and *p_Proteobacteria*. In the Ct group, they accounted for 61.75%, 33.13% and 2.24%, respectively. The percentages were 39.92%, 43.33% and 11.95% in the DM group, and 34.88%, 48.26% and 11.98% in the DM+Q group, respectively. It is evident that the proportion of the dominant phyla in the DM group differed from that in the Ct group. The results are shown in Fig.4.

We also performed a genus-level analysis of the composition of the three groups of rat microbiota. From the analysis of the dominant species in Fig.4, we can conclude that the dominant species is among the four groups. The proportion of the same species also differs within each group. We analyzed the species composition differences among the four groups and ranked them according to mean abundance. Species that exhibited significant differences among the four groups included *g_Bacteroides*, *g_Romboutsia*, *g_Barnesiella*, and others. At the level of species abundance, the DM group had a certain degree of change in the abundance of bacterial genera, and the intervention of quercetin reversed the abundance of some bacterial

genera compared to the Ct group. The heat map illustrating the difference between the groups at the dependent level also visually depicts the variation in the abundance of bacterial genera among the four groups (Fig.4).

Further differences in species composition were revealed through group-to-group comparative analysis (Fig.4). The proportion of *g_Alistipes* in the Ct group was significantly higher than the DM group. Notably, the proportion in the DM+Q group was markedly higher than that in the DM group ($P < 0.05$). Relative to the DM group, *g_Barnesiella* abundance was significantly elevated in both the Ct and DM+Q group, exhibiting a consistent upward trend ($P < 0.05$). Conversely, the proportion of *g_Blautia* in the DM group was significantly higher than that in the Ct group ($P < 0.05$). In the DM+Q group, the abundance of *g_Blautia* decreased significantly compared with the DM group, showing a notable toward the level observed in the Ct group ($P < 0.05$).

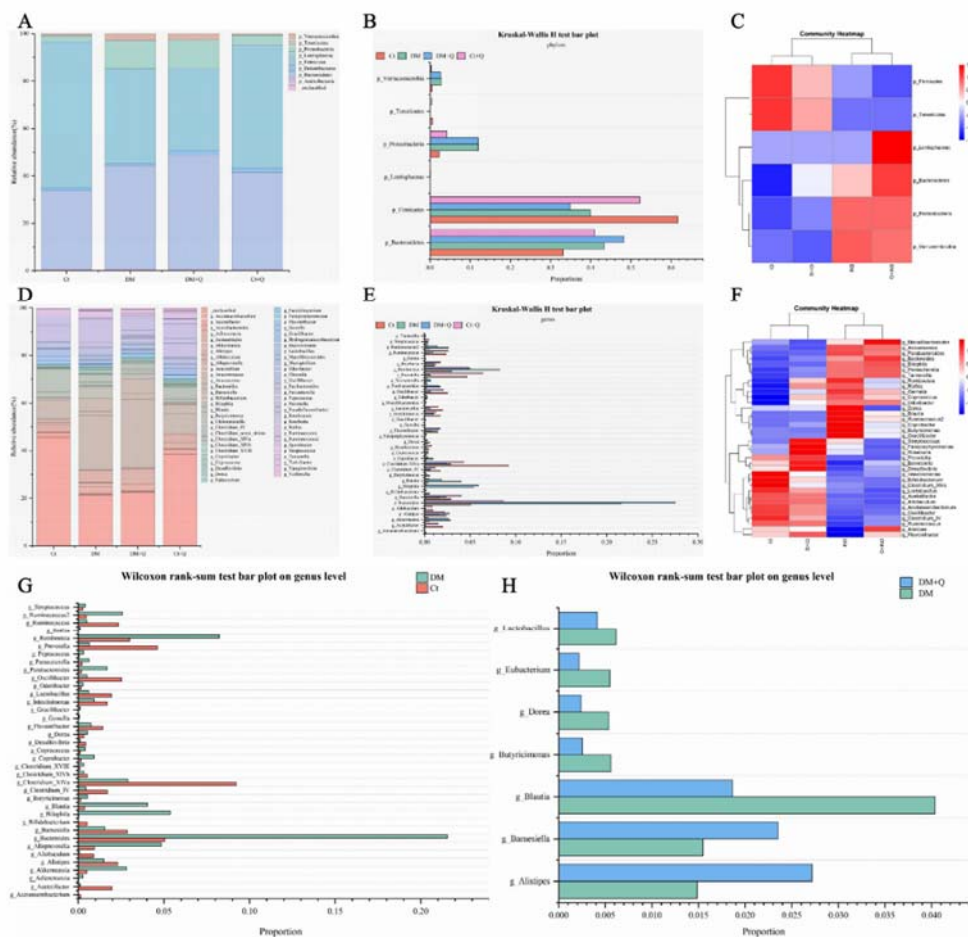


Fig. 4 Gut microbiota community analysis. (A) Community composition Bar map at the phylum level. (B) Comparison of differences among the four groups at the phylum level. (C) Heatmap of species with significant differences in abundance at the phylum level. (D) Community composition Bar map at the genus level. (E) Comparison of differences among the four groups at the genus level. (F) Heatmap of species with significant differences in abundance at the genus level (top 20). (G) Comparison of abundance between Ct and DM groups at the genus level. (H) Comparison of abundance between DM and DM+Q groups at the genus level.

3.2.3 LDA and LEfSe analysis

LDA and LEfSe analyses were performed on the gut microbiota of the three groups to further identify the biomarkers with significant enrichment and difference in abundance across the boundary to medium levels

among the groups. Fig.5 shows the different species at all levels from phylum to genus. LDA analysis showed that a total of 29 significantly different bacteria were enriched in the Ct group, *p_Firmicutes* (LDA value = 5.12), *c_Clostridia* (LDA value = 5.08), *o_Clostridiales* (LDA value = 5.08), *f_Lachnospiraceae* (LDA value = 4.97), and *f_Ruminococcaceae* (LDA value = 4.69) were the top five abundant bacteria. A total of 39 bacteria with significant differences were enriched in the DM group, including *f_Peptostreptococcaceae* (LDA value = 4.41), *g_Romboutsia* (LDA value = 4.41), *g_Blautia* (LDA value = 4.31), *p_Verrucomicrobia* (LDA value = 4.10), and *c_Verrucomicrobiae* (LDA value = 4.10) were the top five abundant bacteria. A total of 46 bacteria with significant differences were enriched in the DM+Q group, *f_Bacteroidaceae* (LDA value = 5.07), *g_Bacteroides* (LDA value = 5.07), *c_Bacteroidia* (LDA value = 4.86), *o_Bacteroidales* (LDA value = 4.86), and *p_Bacteroidetes* (LDA value = 4.86) were the top five abundant bacteria. In conclusion, LDA analysis revealed that the Ct group had higher relative abundance in several bacterial taxa, while the DM group exhibited changes in the relative abundance of these taxa. Moreover, the intervention of DM rats with quercetin could influence the relative abundance of gut flora to a certain extent.

Simultaneously, we can infer from the results that *f_Peptostreptococcaceae*, *g_Romboutsia*, *g_Blautia*, *p_Verrucomicrobia* and *c_Verrucomicrobiae* may be the cause of the keystone species for the occurrence and development of DM. Furthermore, *f_Bacteroidaceae*, *g_Bacteroides*, *c_Bacteroidia*, *o_Bacteroidales*, and *p_Bacteroidetes* may be significant in conferring resistance to DM in the presence of quercetin.

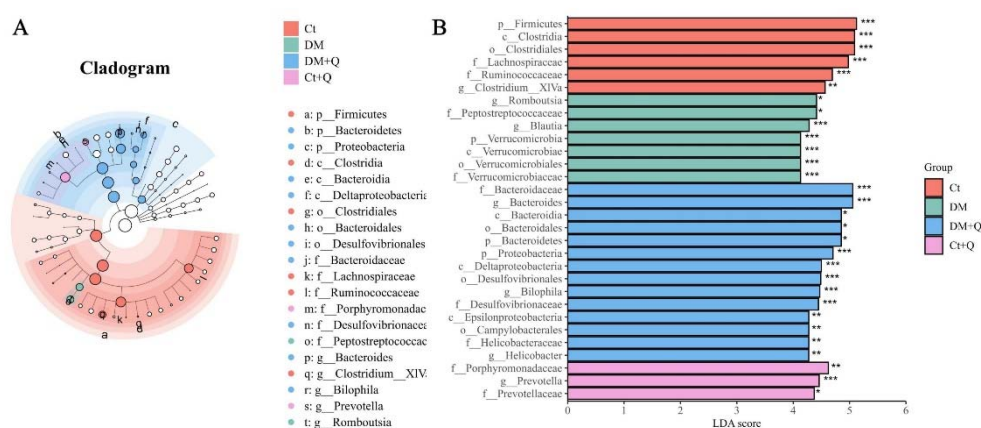


Fig. 5 LDA and LEfSe analysis. (A) Histogram of LDA value distribution. Microbiota with an LDA score greater than 2 were shown in the histogram. The length of the bars represents the effect size of the differing species. (B) Cladogram generated from LEfSe analysis. (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$).

3.2.3 Correlation analysis of gut microbiota and biochemical parameters

To further describe the relationship between the correlation of gut microbiota and biochemical parameters, Spearman correlation coefficient was used to analyze the correlation between these microbiota taxa and biochemical parameters that exhibited significant intergroup differences. As shown in Fig.6, the abundance of *g_Alistipes* exhibited a negative correlation with FBG and TG ($P < 0.05$). The *g_Barnesiella* had a negative trend with AST, FBG, TP, ALT, TG and a positive trend with HDL-C ($P < 0.05$). Furthermore, *g_Blautia* and *g_Butyricimonas* was positively correlated with FBG, AST and ALT, and negatively correlated with HDL-C ($P < 0.05$). The abundance of *g_Dorea* exhibited a positive correlation with FBG, ALT and TG.

g_Eubacterium showed a positive correlation with FBG ($P < 0.05$). Moreover, *g_Latobacillus* was positively correlated with HDL-C and negatively correlated with FBG and ALT ($P < 0.05$). The figure also reflects the correlation between the abundance levels of other bacterial genera and blood glucose and blood lipid levels.

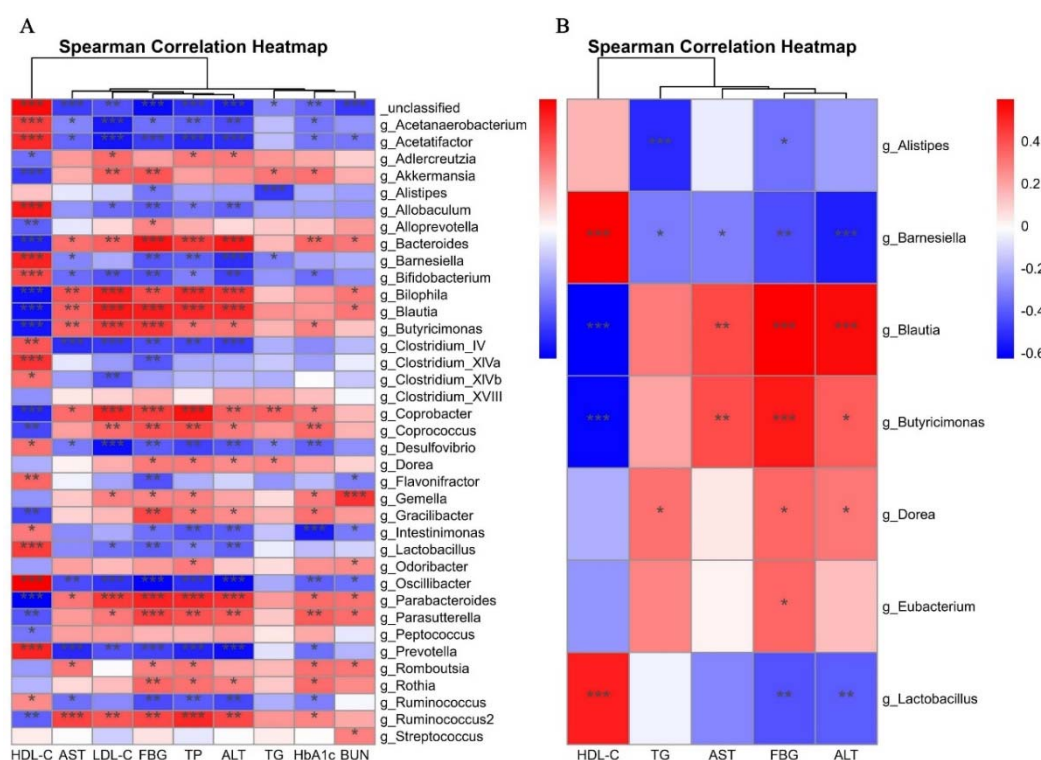


Fig.6 Correlation heatmap showing the functional correlation between gut microbiota and biochemical indicators with both taxa and indicators showing significant intergroup differences. (A) Ct group vs DM group (B) DM group vs DM+Q group. (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$).

3.3 Serum UHPLC-MS untargeted metabolomics analysis

3.3.1 PCA and Orthogonal Partial Least Squares Discriminant Analysis (OPLS-DA) analysis

PCA analysis was performed on the three groups of serum samples and quality control (QC) samples. The PCA outcomes for the serum samples in both cation and anion modes are shown in the Supplementary Materials. The samples from the Ct and DM were distinctly separated, showing good heterogeneity with the anion mode showing more pronounced differences. In addition, the QC samples clustered well, indicating that the experimental system was stable. The OPLS-DA method was used to establish a relationship model between metabolite expression and sample grouping, as shown in Fig.7. In both cation and anion modes, the Ct and DM groups displayed clear separation. And the DM and DM+Q groups displayed clear separation in cation modes. The permutation test for OPLS-DA is a statistical method used to evaluate the stability and reliability of the model, and the relevant results are provided in the Supplementary Materials.

3.3.2 Multivariate statistical analysis

In the cation + anion combined mode, differential metabolites between groups were screened using a two-sample independent t-test. Differential metabolites were screened with the following criteria: $VIP > 1$ obtained from the OPLS-DA model, fold change > 1.5 or < 0.667 , and $P < 0.05$. As shown in the volcano

plots, 1402 differential metabolites were identified in the DM group compared to the Ct group. Among these, 582 metabolites were significantly up-regulated, and 820 were significantly down-regulated. Additionally, 88 differential metabolites were found in the comparison between the DM+Q and DM groups, with 28 metabolites significantly up-regulated and 60 significantly down-regulated (Fig.7).

3.3.3 KEGG enrichment analysis of differential metabolites

The metabolic pathways were filtered using a topological analysis with an Impact > 0.1 and an enrichment analysis with a $P < 0.05$. The results are presented in the form of bubble plots in Fig.7. A total of 13 metabolic pathways were significantly altered between the DM group and the Ct group, with the main pathways affected being D-Arginine and D-ornithine metabolism, Glycerophospholipid metabolism, Arginine and proline metabolism, among others. Additionally, 7 significantly altered metabolic pathways were identified in the differential metabolites between the DM+Q group and the DM group, with the main pathways affected being Sphingolipid metabolism, Glycerophospholipid metabolism, Linoleic acid metabolism, among others.

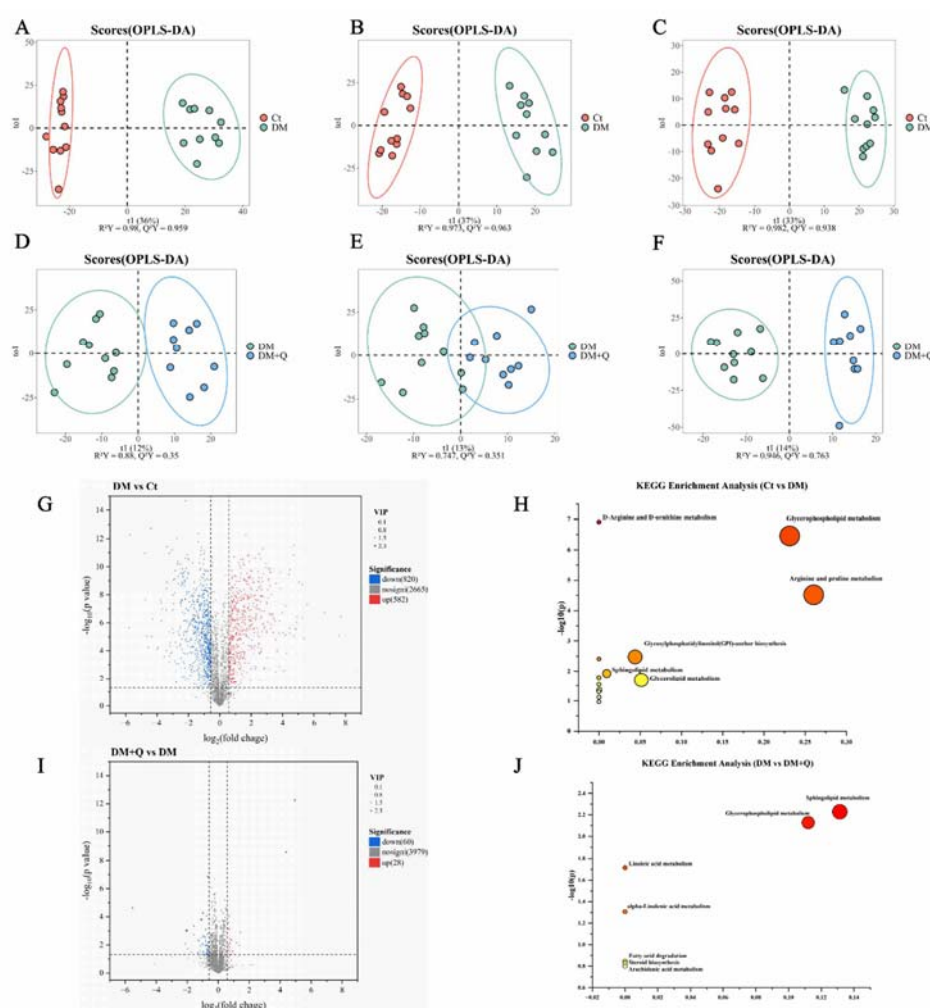


Fig. 7 HPLC-MS untargeted metabolomics analysis. (A, B, C) The OPLS-DA map of Ct and DM in the positive and negative ion mode. (D, E, F) The OPLS-DA map of DM and DM+Q in the positive and negative ion mode. (G) Volcano plot of differences (Ct VS DM). (H) Potential metabolite-related pathways affected by quercetin in DM mice (Ct VS. DM). (I) Volcano plot of differences (DM VS DM+Q). (J) Potential metabolite-related pathways affected by quercetin in DM mice (DM VS.DM+Q).

3.4 Combined analysis of metabolomics and gut microbiota

Correlation heat maps illustrated the relationships between different metabolites and gut microbiota, highlighting the functional link between microbiota composition and body metabolism. In the DM/Ct comparison, as shown in Fig. 8, *g_Alistipes* negatively correlated with metabolites like PC (16:1(9Z)/14:0). *g_Barnesiella* was positively correlated with PC(P-18:0/20:5(5Z,8Z,11Z,14Z,17Z)), but negatively with others like PC (16:1(9Z)/14:0). In the DM+Q/DM comparison, as shown in Fig. 8, *g_Alistipes* was found to be positively correlated with up-regulated metabolites including CDP-DG(18:1(9Z)-O(12,13)/i-13:0), pyroglutamylalanine, TG(16:1(9Z)/14:0/16:1(9Z)), CE(20:4), 3-Hydroxycapric acid, and CE(18:1), and negatively correlated with down-regulated metabolites such as Pyrazolone, Lyso PC(18:1/0:0), 1,17-Diamino-4,9,13-triazaheptadecane, 4-(2'-carboxyphenyl)-4-oxobutyryl-CoA, PS(18:1(11Z)/14:0), TG(15:0/20:0/18:2(9Z,12Z)), TG(18:0/20:4(5Z,8Z,11Z,14Z)/20:3n6), LysoPA(21:0/0:0), LysoPE(20:1(11Z)/0:0), PE-NM e(20:2(11Z,14Z)/20:0), SM(d18:2(4E,14Z)/24:0) and SM(d18:1/24:1). *g_Barnesiella* negatively correlated with SM(d18:1/24:1) and 2,3-diketogulonate but was positively linked to PA(2:0/20:5(7Z,9Z,11E,13E,17Z)-3OH (5,6,15)) and glutamine betaine.

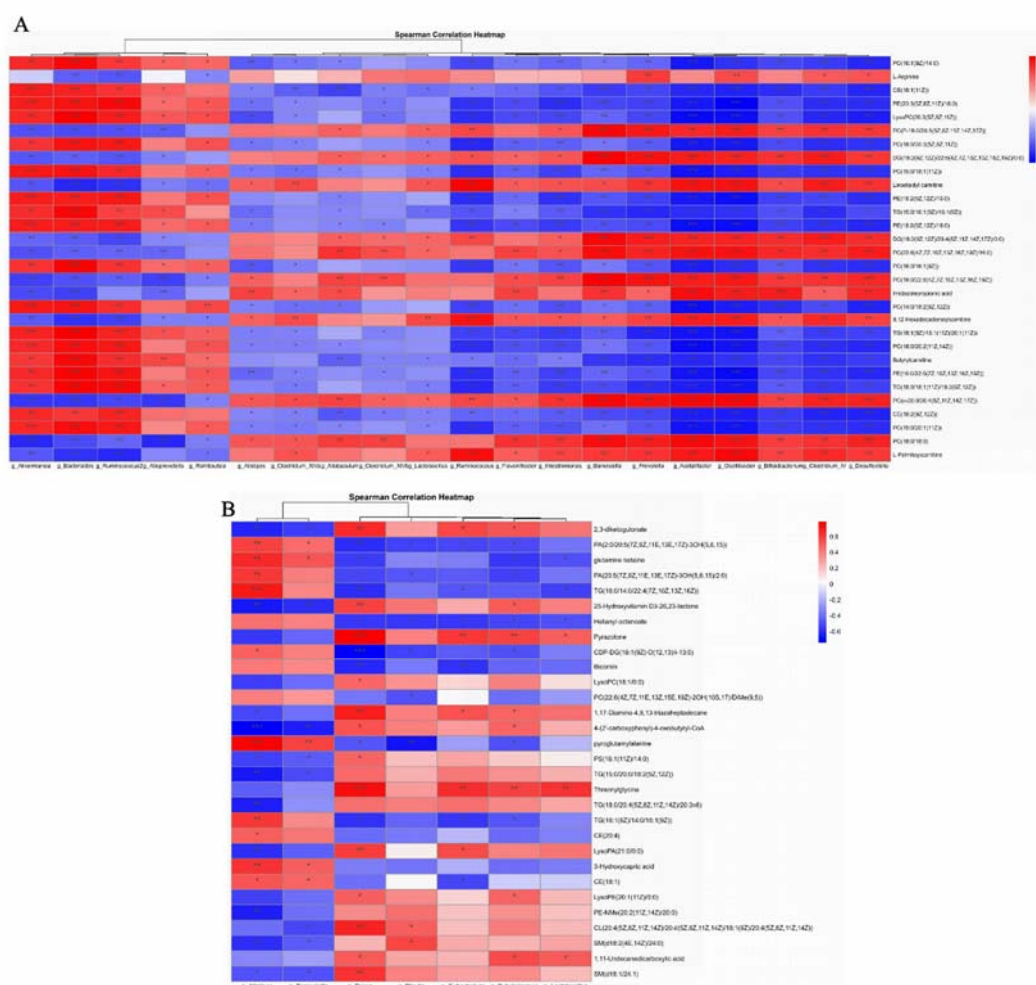


Fig. 8 Heatmap of the Spearman's correlation between differential metabolites and differential microbiota at genus level. (A) Ct group VS. DM group. (B) DM group VS. DM+Q group. (Red squares indicated significant positive correlations, blue squares indicated significant negative correlations and white squares indicated non-significant correlations. (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$).

4. Discussion

In this study, we evaluated the effects of quercetin intervention on diabetic rats. The significant elevation of FBG and HbA1c in the DM group indicates that the rats exhibit typical symptoms of T2DM. Moreover, hyperlipidemia, hepatic lipid accumulation, and liver function impairment were observed in the DM group. T2DM affects all systems in the body, potentially leading to various diseases, such as hyperglycemia and metabolic dysfunction-associated steatohepatitis (MASH). Population-based studies show that MASH is closely associated with T2DM, with a global pooled prevalence of 65.33% (95% CI: 62.35%–68.18%) among diabetic patients [17]. Previous studies have shown that quercetin can promote insulin secretion, improve insulin resistance, lower blood lipid levels, inhibit inflammation and oxidative stress, alleviate hepatic lipid accumulation, and regulate gut microbiota disorders in animal models [8]. Our results indicate that quercetin can significantly reduce blood glucose levels, improve lipid profiles, alleviate hepatic lipid accumulation, and enhance liver function. The results prove that quercetin intervention can exert effects against glucose and lipid metabolic disorders in diabetic rats.

Increasing clinical evidence suggests that there are changes in the structure and homeostasis of the intestinal microbiota in T2DM patients. A systematic review revealed that microbial diversity scores were lower in both prediabetes and T2DM cohorts in 86% of the analyzed studies [18]. Another cross-sectional study found that higher microbiome alpha diversity was related to lower T2DM prevalence [19]. Polyphenolic compounds have been found to have effects on the regulation of intestinal microbiota, with quercetin being the main component at work [11]. Quercetin can improve microbial community diversity and increase intestinal probiotic levels in type 2 diabetic mice [20]. In the present study, the observed Chao1 and ACE indices were significantly increased in DM+Q groups compared to those of the DM group, indicating that quercetin remarkably improved the microbiota diversity and homogeneity in diabetic rats. The intestinal canal is predominantly inhabited by the phyla *p_Firmicutes*, *p_Bacteroidota*, *p_Proteobacteria*, and *p_Actinobacteriota* [21].

Changes in the abundance of specific gut microbiota are often associated with several diseases. Significant alterations in the gut microbiota have been observed among individuals with prediabetes, newly diagnosed T2DM, and normal glucose tolerance [21]. However, considerable uncertainty remains in this field of study. A systematic review has shown a significant decrease in *p_Bacteroidetes* among individuals with T2DM [22]. In contrast, a significantly higher proportion of *p_Bacteroidetes* has been reported in subjects with T2DM in a cohort study [23]. Our results indicate an increasing trend of *p_Bacteroidetes* in diabetic rats. Host dietary patterns, genetic characteristics, and environmental factors can collectively shape the composition and structure of the gut microbiota [24]. Different microbial taxa exhibit distinct or even opposing roles in metabolic diseases. These factors may account for the contradictory findings observed across different studies [25]. The contradictory observations indicate that the analysis of the microbiota at the phylum level might not be sufficient. Investigations conducted at deeper taxonomic levels are more conducive to precisely elucidating the intrinsic associations between the gut microbiota and T2DM [26].

At the genus level, our analysis revealed significant differences in the relative abundance of *g_Alistipes* and *g_Barnesiella* among groups. Notably, the relative abundance of these genera was reduced in diabetic rats following quercetin treatment. *g_Alistipes* has been shown to mediate the delivery of immunomodulatory lipids and modulate the host plasma lipidome [27]. The abundance of *g_Alistipes* was positively correlated with IL-10 and negatively correlated with insulin resistance and serum FBG levels in T2DM mice. A clinical study identified *g_Alistipes* as one of the potential bacterial biomarkers associated with gestational diabetes, with lower abundance in patients [8]. Resveratrol is also a polyphenolic compound and shares certain structural and functional similarities with quercetin [28]. Resveratrol increases the abundance of *g_Alistipes*, an effect similar to that of anti-diabetic drugs [29]. A comparative study between Han and Mongolian populations indicated that *g_Barnesiella* is closely related to T2DM in Mongolian patients [30]. The abundance of *g_Barnesiella* was reduced in patients with impaired glucose regulation or T2DM [31, 32]. *g_Barnesiella* produces acetate, which increases the expression of fibroblast growth factor 21 by inhibiting histone deacetylase 9, ultimately improving T2DM [32]. The screening of puerarin from Gegen Qinlian decoction in a gut microbiota-dependent manner improved hyperglycemia and liver metabolic disorders by promoting the growth of *g_Bacteroidetes* [32]. Both *g_Alistipes* and *g_Barnesiella* are members of the Bacteroidetes phylum. Quercetin can enhance the relative percentage of *p_Bacteroidetes* in mice fed a high-fat diet. *g_Blauti* have been reported in a positive association with T2DM, which is consistent with the findings of our study [33]. Dried chicory root intervention can reduce *g_Blauti* abundance, and baseline *g_Blauti* levels affect T2DM high-risk individuals' metabolic response to the intervention [34]. *Grifola frondosa* can increase the abundance of probiotics such as *g_Blauti*, thereby exerting a hypoglycemic effect and improving diabetic symptoms in T2DM mice [35].

To be specific, we found that quercetin may affect the phenotype of T2DM by metabolic pathways. KEGG pathway analysis showed SM(d18:1/24:1) was enriched in the Sphingolipid metabolism. It has been shown that Sphingolipid metabolism pathway was closely related to the T2DM [36]. SM(d18:1/24:1) is a specific type of sphingomyelin (Sphingolipid). It is an important component of the cell membrane and is involved in various physiological processes, such as cell signaling and apoptosis. Some studies have revealed that SM(d18:1/24:1) has an effect on glucose homeostasis and lipid metabolism [37]. Previous studies have found that quercetin can improve liver cancer and alleviate depressive emotions by affecting key enzymes and metabolites in sphingolipid metabolism [13, 38].

Our association analysis found that *g_Alistipes* and *g_Barnesiella* were associated with FBG and HbA1c. On the other hand, *g_Alistipes* and *g_Barnesiella* were associated with SM(d18:1/24:1) suggesting that quercetin may regulate glucose metabolism in diabetic rat through the microbiota. *Alistipes shahii* is a formally recognized species of the *g_Alistipes*. This bacterium has been confirmed to encode glucosylceramidase, a key enzyme in sphingolipid metabolism that hydrolyzes glucosylceramide into glucose and ceramides. Relevant studies have verified that

Alistipes shahii exerts anti-inflammatory effects in Crohn's disease by regulating host sphingolipid metabolism [39]. These findings suggest that *g_Alistipes* may regulate sphingolipid metabolism in a similar

manner in the context of T2DM. Therefore, further studies are needed to clarify the specific functional pathways and molecular targets through which *g_Alistipes* modulates sphingolipid metabolism in T2DM. Such research will provide critical theoretical support for understanding the therapeutic potential of quercetin in T2DM.

Quercetin and its derivatives are flavonoid compounds derived from natural plandiabetest sources, widely available, and relatively non-toxic. Their application in the clinical treatment of can alleviate adverse reactions in patients and significantly reduce treatment costs. Intervention studies in patients with T2DM are still needed to determine the effects of quercetin and the appropriate intervention dosage. Therefore, developing diabetes nutritional supplements with quercetin as the primary functional ingredient and deeply exploring the mechanisms by which quercetin can prevent and treat T2DM holds great social value and scientific significance.

5. Conclusions

This study proposed the gut microbiome as the target of action and investigated the potential mechanisms by which quercetin improved the symptoms of T2DM within an animal model. Our results indicated that the supplementation of quercetin can alleviate glucose and lipid metabolism disorders, reduce hepatic lipid accumulation, and improve hepatic function in diabetic rats. Gut microbiota analysis demonstrated that quercetin could significantly modulated both beneficial and harmful bacteria. Moreover, untargeted metabolomics analysis revealed that quercetin intervention altered the metabolites of diabetic rats, resulting in significant decreases in SM(d18:1/24:1). In summary, quercetin has a good anti-diabetic effect on diabetic rats by remodeling the intestinal microbiota and altering serum metabolites.

Conflict of interest

The authors declare no competing financial interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version.

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