Clinical and Experimental Obstetrics & Gynecology

Clin. Exp. Obstet. Gynecol. **2025**; 52(12): 45098
https://doi.org/10.31083/CEOG45098

Original Research

Yam Polysaccharide Ameliorates High-Fat and Fructose Diet-Induced Gestational Diabetes Mellitus in Mice via Gut Microbiota Remodeling

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Academic Editors: Natasha Singh and Laura Avagliano
Submitted: 17 July 2025 Revised: 25 September 2025 Accepted: 13 October 2025 Published: 22 December 2025

Abstract

Background: Yam Polysaccharide (YP) is a major bioactive component extracted from the common yam rhizome and has been shown to have an antidiabetic effect. Previous research has demonstrated the association between gut microbiota (GM) and gestational diabetes mellitus (GDM); however, whether GM is essential for mediating the antidiabetic effects of YP in GDM remains unclear. **Method**: A high-fat and fructose diet (HFD) was administered to mice before and after pregnancy to induce GDM. An oral glucose tolerance test (OGTT) was performed, and the homeostatic model assessment of insulin resistance (HOMA-IR) was calculated to evaluate glucose metabolism. The GM composition was analyzed using 16S rRNA sequencing. **Results**: During pregnancy, mice fed an HFD exhibited significant weight gain accompanied by impaired glucose tolerance. These metabolic disturbances were alleviated by YP treatment. Furthermore, consuming an HFD induced marked alterations in GM diversity compared to the control group, characterized by increased abundance of *Alloprevotella* and decreased abundance of the *Lachnospiraceae* NK4A136 group. Importantly, YP administration reversed these HFD-induced microbial changes. **Conclusions**: These findings suggest that modulation of the GM is one mechanism underlying the antidiabetic effects of YP in GDM.

Keywords: gestational diabetes mellitus; gut microbiota; 16S rRNA sequencing; Yam Polysaccharide

1. Introduction

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance that is recognized during pregnancy [1]. A global epidemiology study reports a prevalence of GDM at 17.8% [2]. Additionally, a meta-analysis involving 79,064 Chinese participants found an incidence rate of 14.8% [3]. GDM increases the risks of complications such as eclampsia, macrosomia, induced labor, preterm delivery, and cesarean section [4]. Moreover, pregnant women with GDM and their offspring are at a higher risk of developing type 2 diabetes mellitus (T2DM) [5,6] and are more susceptible to cardiovascular diseases [7,8] in the long term. Thus, the prevention and management of GDM has become one of the most important public health issues that needs to be addressed.

The mechanisms underlying the onset and progression of GDM have not been fully understood. Increasing evidence suggests that an imbalance of the gut microbiota (GM) may play a significant role in the development of metabolic disorders, obesity, and diabetes. GM is essential for host physiology, as it regulates nutrient metabolism, maintains the integrity of the intestinal barrier, modulates immune responses, and produces bioactive metabolites such as short-chain fatty acids (SCFAs). Through these functions, GM contributes to energy homeostasis, systemic immunity, and overall metabolic health. It has been observed that the composition of GM changes during pregnancy. A prospective cohort of 91 Finnish women found that GM obtained in the third trimester showed increased diversity but reduced richness. There was also a notable increase in Proteobacteria in pregnant women compared to non-pregnant controls [9]. Crusell *et al.* [10] demonstrated that GM composition in women with GDM, during and after pregnancy, resembled the altered microbiota seen in non-pregnant individuals with T2DM. Genera such as *Desulfovibrio* and *Collinsella* are enriched in patients with GDM and T2DM [10], with *Collinsella* specifically linked to higher fasting insulin levels and homeostatic model assessment for insulin resistance (HOMA-IR) [11]. Furthermore, bacteria such as *Bacteroides dorei* [12], *Blautia* [13], *Klebsiella variicola* [14], and *Ruminococcaceae* [15] have been identified as risk factors for GDM, while *Bifidobacterium* [14], *Akkermansia* [16], and *Faecalibacterium* [17] are considered protective. These bacteria play active roles in glucose and lipid metabolism and are closely associated with insulin resistance, potentially explaining how changes contribute to the development of GDM.

Chinese yam (*Dioscorea opposita*) has been used for centuries in traditional Chinese medicine and as a functional health food. Yam Polysaccharide (YP), the primary bioactive component found in the Chinese yam, is a high-molecular-weight polymer of monosaccharides (such as glucose, galactose, and mannose linked together in a complex structure. YP can be industrially extracted and purified, exhibiting multiple biological activities, including antioxidant, anti-inflammatory, and metabolic regulatory effects. These properties make YP a crucial compound for examining the therapeutic potential of Chinese yams [18]. Previous research has found that YP improves abnormal lipid metabolism in both animal models and in patients with T2DM [19]. However, the impact of YP on GDM and its underlying mechanism remains unclear.

In the present study, a high-fat and fructose diet (HFD)-induced GDM mouse model was employed to evaluate the effect of YP on GDM. Furthermore, changes in GM were assessed to explore the potential mechanism through which YP may exert therapeutic effects in GDM.

2. Materials and Methods

2.1 Animal Model

Six-week-old C57BL/6 mice were purchased from the Guangdong Medical Laboratory Animal Center (Guangzhou, Guangdong, China). All animal experiments were approved by the Ethics Committee of the First Affiliated Hospital of Guangdong Pharmaceutical University. The female mice were randomly divided into three groups: (1) the control group, which received a normal diet (10 kcal% fat, 3.85 kcal/g; Guangdong Medical Laboratory Animal Center; batch No. D12450B) and untreated drinking water; (2) the model group, which received a high-fat diet (45 kcal% fat, 4.73 kcal/g; Guangdong Medical Laboratory Animal Center; batch No. D12450B) and drinking water supplemented with 10% (w/v) fructose (Fru, 4 kcal/g; Yongjin Biotechnology Co., Guangzhou, Guangdong, China; batch No. BWJ4341-2016). This group was also named the HFD group; and (3) the treatment group (HFD + YP), which received a daily oral gavage of YP powder (Shanghai Yuanye Bio-Technology Co., Shanghai, China; batch No. S24912) dissolved in sterile water and administered while maintained on an HFD, starting after mating. The dosage of YP was 200 mg/kg body weight per day. The control group and HFD groups were given an equal amount of sterile water by gavage after mating. After a six-week dietary intervention, female mice were mated with lean male mice. Mating was confirmed by the presence of a vaginal mucus plug the following morning, which was designated as gestational day (GD) 0. Based on pilot experiments and power analysis, each group required n = 6 mice to achieve 80% power to detect a 30% difference at significance levels of $\alpha = 0.05$.

2.2 Measurement of Serum Glucose and Insulin

Mice underwent an oral glucose tolerance test (OGTT) at GD15 after a 12-hour fast. Each mouse was orally gavaged with glucose at a dose of 2 g/kg body weight, prepared in normal saline. Blood samples were collected from the vein at 0, 30, 60, 90, and 120 minutes after glucose administration to measure the glucose concentration.

Blood glucose levels were quantified using a glucose assay kit (Solarbio, Beijing, China; batch No. BC2495) in accordance with the manufacturer's protocol, which follows the glucose oxidase method. Serum insulin levels were measured with a mouse ultrasensitive insulin ELISA kit (Wuhan Colorful Gene Biotech Co., Ltd., Wuhan, China; batch No. JYM0351Mo). The HOMA-IR was calculated using the following formula: HOMA-IR = (fasting glucose $\times$ fasting insulin)/22.5.

2.3 Cell Culture, Adipogenesis Induction, and Glucose Uptake Test

3T3-L1 murine preadipocytes were purchased from Cas9X Biotechnology Company (Suzhou, Jiangsu, China; batch No. TCM-C702). This cell line has been authenticated by short tandem repeat analysis, morphological observation, and adipogenic induction, and it tested negative for mycoplasma contamination. 3T3-L1 cells in the logarithmic growth phase were seeded into culture vessels at a density of 2.0×10^4 cells/cm^2 at 37 °C and 5% CO_2 until reaching 90–100% confluency. Adipogenic differentiation kit (Cas9X biotechnology; Suzhou, Jiangsu, China; batch No. EFMX-D102) used for adipogenic induction by alternative replacement of the induction and maintenance medium. The timing for terminating cell induction was determined based on the number and size of lipid droplets formed during the process, followed by staining for identification. Cells were first fixed with 4% neutral formaldehyde solution at room temperature for 30 to 60 min, stained with red oil O solution for 30 min, and evaluated under a microscope. The glucose tolerance of 3T3-L1 adipocytes was assessed by performing glucose uptake tests under an insulin stimulation at a dosage of 100 nM for 30 min, using the Glucose Uptake-Glo^{TM} assay kit (Promega, Madison, WI, USA; batch No. J1341).

2.4 16S rRNA Sequencing

Fecal samples were collected at GD16 in individual sterilized cages and immediately frozen in liquid nitrogen. DNA was extracted according to the instructions of the DNA extraction kits (TaKaRa Bio, Beijing, China; batch No. 9765). The integrity and purity of the DNA were detected by 1% agarose gel electrophoresis, and the concentration and purity of the DNA were detected by the NanoDrop One microvolume spectrophotometer (ThermoFisher Scientific, Waltham, MA, USA). PCR amplification and product electrophoresis were performed using genomic DNA as a template, and primers with barcodes

and Premix Tag (TaKaRa Bio; Beijing, China; batch No. RR004A) were used for PCR amplification based on selected sequencing regions. Gene Tools Analysis Software (Cambridge, UK; Version 4.03.05.0, SynGene) was used to quantify PCR product concentrations. The volume of each sample was adjusted to ensure equal mass, and the PCR products were pooled. Mixed PCR products were purified using the E.Z.N.A. Gel Extraction and Gel Recovery Kit (Omega Bio-Tek, Guangzhou, Guangdong, China; batch No. D2500). Target DNA fragments were eluted with TE buffer. Library construction was then performed using the NEBNext® Ultra™ DNA Library Prep Kit for Illumina® (New England Biolabs, Ipswich, MA, USA; batch No. E7645) standard process. The high-throughput sequencing platform HiSeq was utilized for online sequencing, and the raw image data file was converted into a raw sequencing dataset (Raw Reads) through base recognition (Base Calling) analysis. The results were stored in the FASTQ file format, which contains the sequencing sequence (Reads) and its corresponding quality information. Alpha diversity, which reflects the richness and evenness of microbial communities within a sample, was evaluated using the Shannon and Simpson indices. Beta diversity, which measures compositional differences between microbial communities across samples, was evaluated using Principal Coordinates Analysis (PCoA) based on the Bray-Curtis distance matrix. Additionally, Analysis of Similarities (ANOSIM) was employed to determine the significance of differences in microbial communities between groups. Analysis of species differences across multiple groups was based on Kruskal-Wallis rank sum test. The false discovery rate (FDR) was used for multiple-testing correction.

2.5 Statistical Analysis

The data are presented as mean $\pm$ SD. We validated the assumption of normality using both the Shapiro-Wilk test and visual inspection of the quantile-quantile (Q-Q) plot. The homogeneity of variances was assessed using the Brown-Forsythe test. A p-value greater than 0.05 indicated that the assumptions were met, and a one-way analysis of variance (ANOVA) was used to detect statistical significance, followed by Tukey's multiple comparisons test. A Kruskal-Wallis rank sum method was used for non-parametric test, followed by Dunn's multiple comparisons test. A p-value less than 0.05 was considered statistically significant. Statistical analysis and graph plotting were conducted with GraphPad Prism (version 9, GraphPad software Inc., San Diego, CA, USA).

3. Results

3.1 The Impact of HFD on Glucose Metabolism in Pregnant Mice

The experimental protocol for the animal study is shown in Fig. 1A. The HFD intervention was initiated six weeks before pregnancy and was maintained throughout the pregnancy. Fasting blood glucose was measured, and an OGTT was performed before mating to exclude individuals with pre-existing diabetes. All variables of interest satisfied the assumption of normality according to the Shapiro-Wilk test (all $p > 0.3$). The Brown-Forsythe test confirmed that the assumption of homogeneity of variance was not violated (all $p > 0.4$). Consequently, ANOVA was applied for group comparisons. Significant weight gains in the pre-pregnancy stage were observed in groups that underwent HFD treatment, including the HFD group and HFD + YP group, compared to the control group (Fig. 1B). Moreover, HFD-treated mice exhibited a significant weight gain during early and mid-pregnancy (Fig. 1C). An OGTT at GD15 was conducted to determine the changes in glucose tolerance during pregnancy. The area under the curve (AUC) for the OGTT of the HFD group was significantly increased compared to that in the control group (Fig. 1D,E). To further assess the effects of HFD on glucose metabolism, the level of fasting serum glucose and insulin was measured at GD16 and used for calculating HOMA-IR. Compared to the control group, mice in the HFD group had a higher HOMA-IR (1.54 ± 0.76 vs. 1.40 ± 0.94). These findings supported that mice subjected to HFD were more susceptible to insulin resistance, exhibited glucose intolerance, and developed GDM.

3.2 The Effect of YP on Alleviating Dysfunctional Glucose Metabolism

Compared with the HFD group, the YP-treated group exhibited significantly lower levels of blood glucose at 30 min, 60 min, and 90 min during the OGTT, along with a smaller AUC (Fig. 1D,E). A notable decrease in HOMA-IR was also observed in the HFD + YP group compared to the HFD group (1.00 ± 0.50 vs. 1.54 ± 0.76). These findings suggested that YP may alleviate impaired glucose tolerance and insulin resistance in the GDM model. Additionally, the addition of YP did not significantly induce weight loss in the pregnancy compared to the HFD group (Fig. 1C).

Additionally, an *ex vivo* experiment was performed to evaluate the impact of YP on insulin resistance. Murine preadipocyte 3T3-L1 were induced to differentiate into adipocytes (Fig. 2A). Dexamethasone inhibited glucose uptake in adipogenically induced 3T3-L1 cells, indicating successful establishment of an insulin resistance model (Fig. 2B). YP was found to alleviate dexamethasone-induced impairment of glucose uptake in a dose-and time-dependent manner (Fig. 2C,D).

3.3 The Influence of HFD on the Composition of GM in Pregnant Mice

Analysis of alpha diversity of GM among the three groups showed that the Shannon index was significantly higher in the HFD group than in the control group, whereas the Simpson index was lower. These findings indicated that the HFD-induced GDM model exhibited increased richness

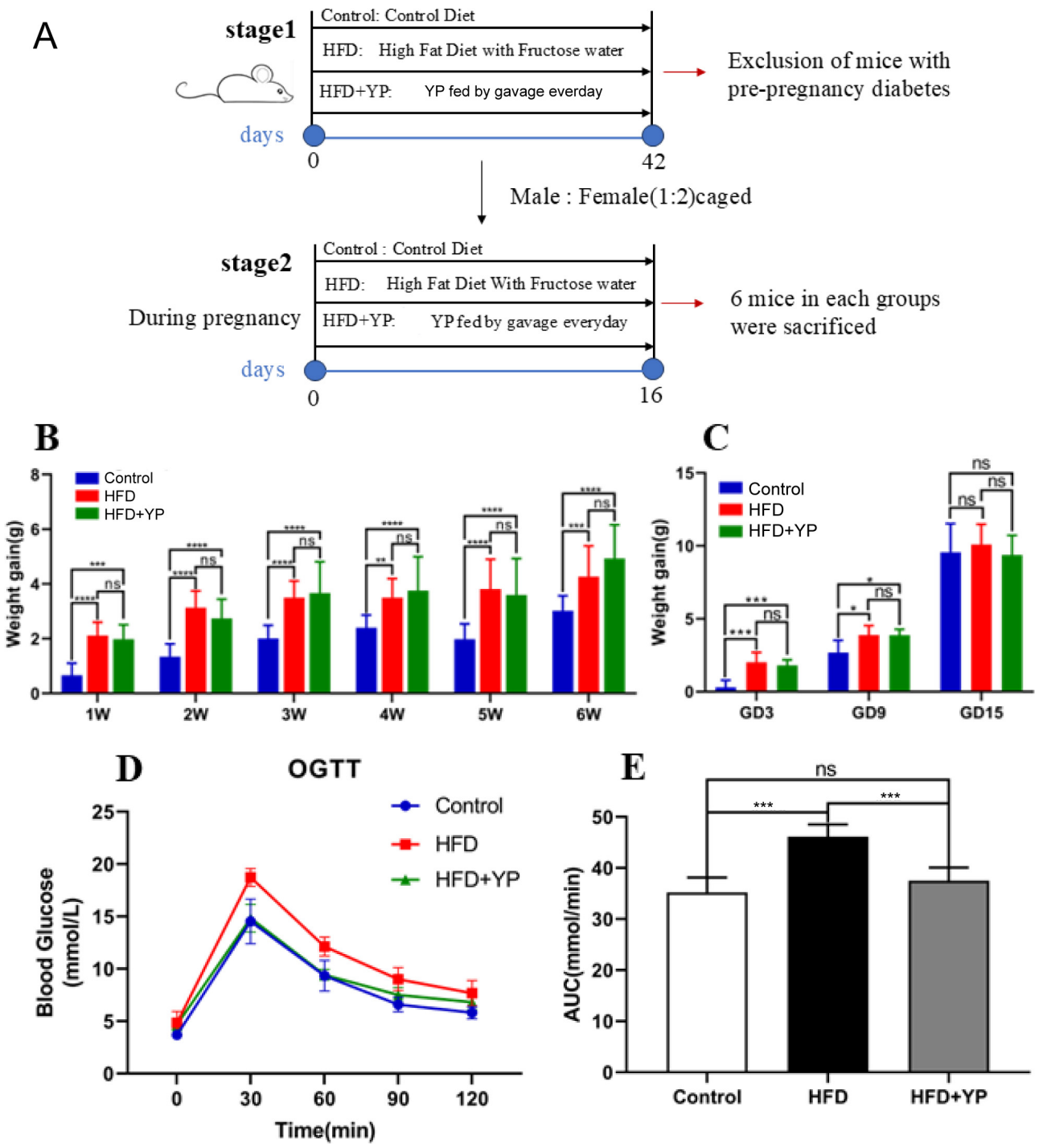

Fig. 1. YP inhibits the progression of GDM. (A) Schematic design of the experiment. (B) Weight gain during intervention before pregnancy. (C) Weight gain during pregnancy. (D) Oral glucose tolerance tests (OGTT). (E) AUC of OGTT. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$; ns, not significant. GDM, gestational diabetes mellitus; AUC, area under the curve; YP, Yam Polysaccharide; HFD, high-fat and fructose diet.

and decreased evenness of microbial communities compared with the control group. (Fig. 3A,B). In addition, YP prevented the HFD-induced increase in alpha diversity (Fig. 3A,B). Subsequently, the beta diversity of microbial communities among the three groups was investigated using PCoA, which revealed three distinct clusters corresponding to the intervention groups. The separation between the HFD and control groups was particularly pronounced, indicating HFD-induced alteration in GM composition. Importantly, YP administration induced additional alterations in the microbial community structure across samples (Fig. 3C).

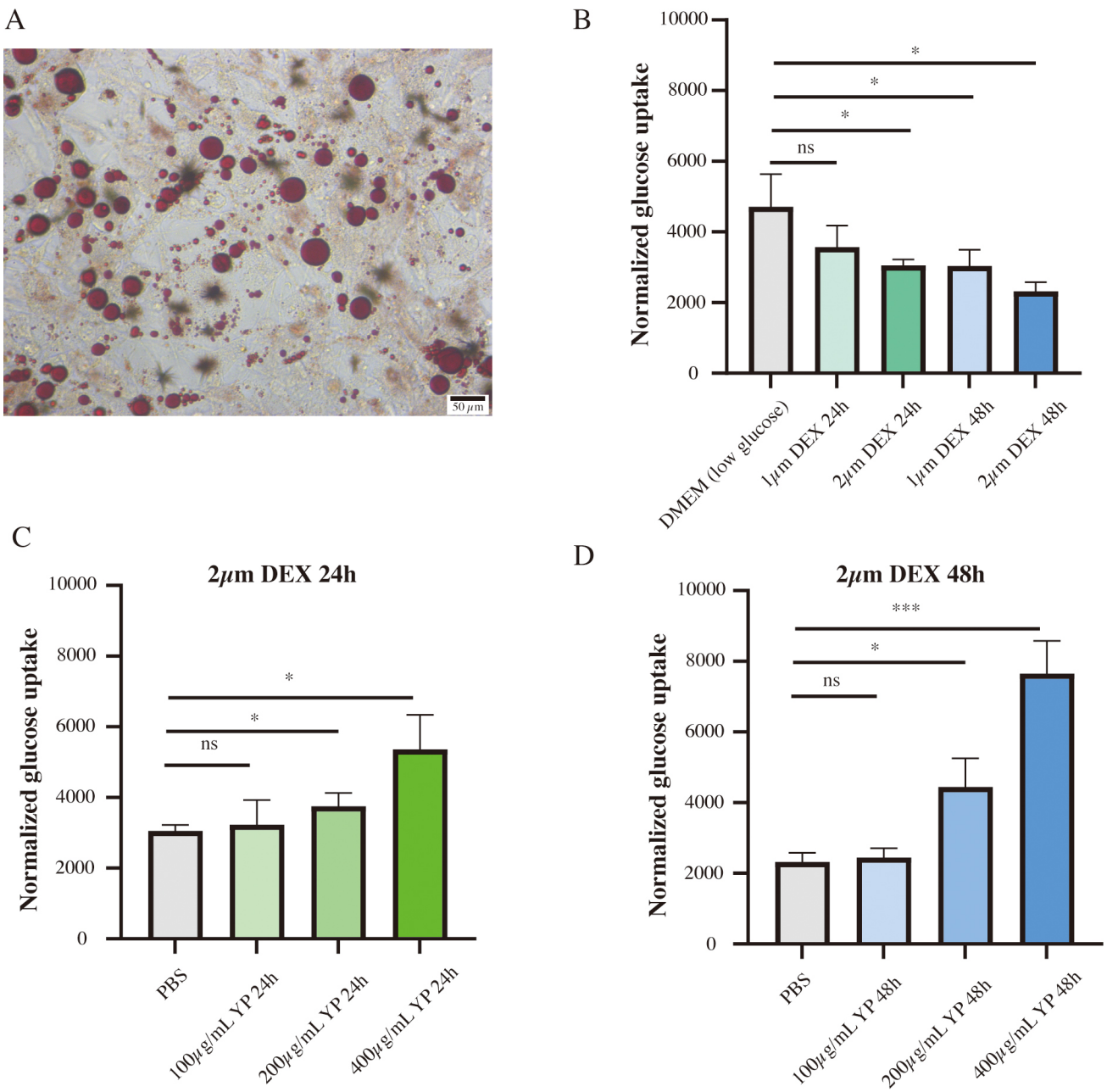

Fig. 2. YP alleviated dexamethasone (DEX)-induced impaired glucose uptake in 3T3-L1 adipocytes. (A) Red oil O staining demonstrated the adipogenesis induction in 3T3-L1 cells, scale bar: 50 μm. (B) DEX inhibited glucose uptake in 3T3-L1 adipocytes compared to control group. (C,D) YP enhanced glucose uptake in 3T3-L1 adipocytes incubated with 2 μm DEX compared to control group. ns, not significant; DMEM, Dulbecco's Modified Eagle Medium; PBS, phosphate buffered saline, * $p < 0.05$, *** $p < 0.001$.

We analyzed the relative abundance of species across the three groups at the phylum level (Fig. 3D). The Firmicutes/Bacteroidetes (F/B) ratio was increased in both the HFD and HFD + YP groups compared with the control group (Fig. 3D). An increased F/B ratio is commonly observed in obese individuals [20]. The elevated F/B ratio in the HFD and HFD + YP groups indirectly reflects the effect of the metabolic alteration induced by HFD treatment and is consistent with the finding that YP did not attenuate the HFD-induced weight gain in pregnant mice. At the genus level, the relative abundance of *Alloprevotella* decreases in the HFD group compared with the control group but increases in the HFD + YP group. In contrast, the relative abundance of *Lachnospiraceae* NK4A136 group increased in the HFD group but declined with YP treatment (Fig. 3E,F). These findings suggest that *Alloprevotella* and *Lachnospiraceae* NK4A136 group may be potential microbial targets through which YP alleviates GM dysbiosis and abnormal glucose metabolism.

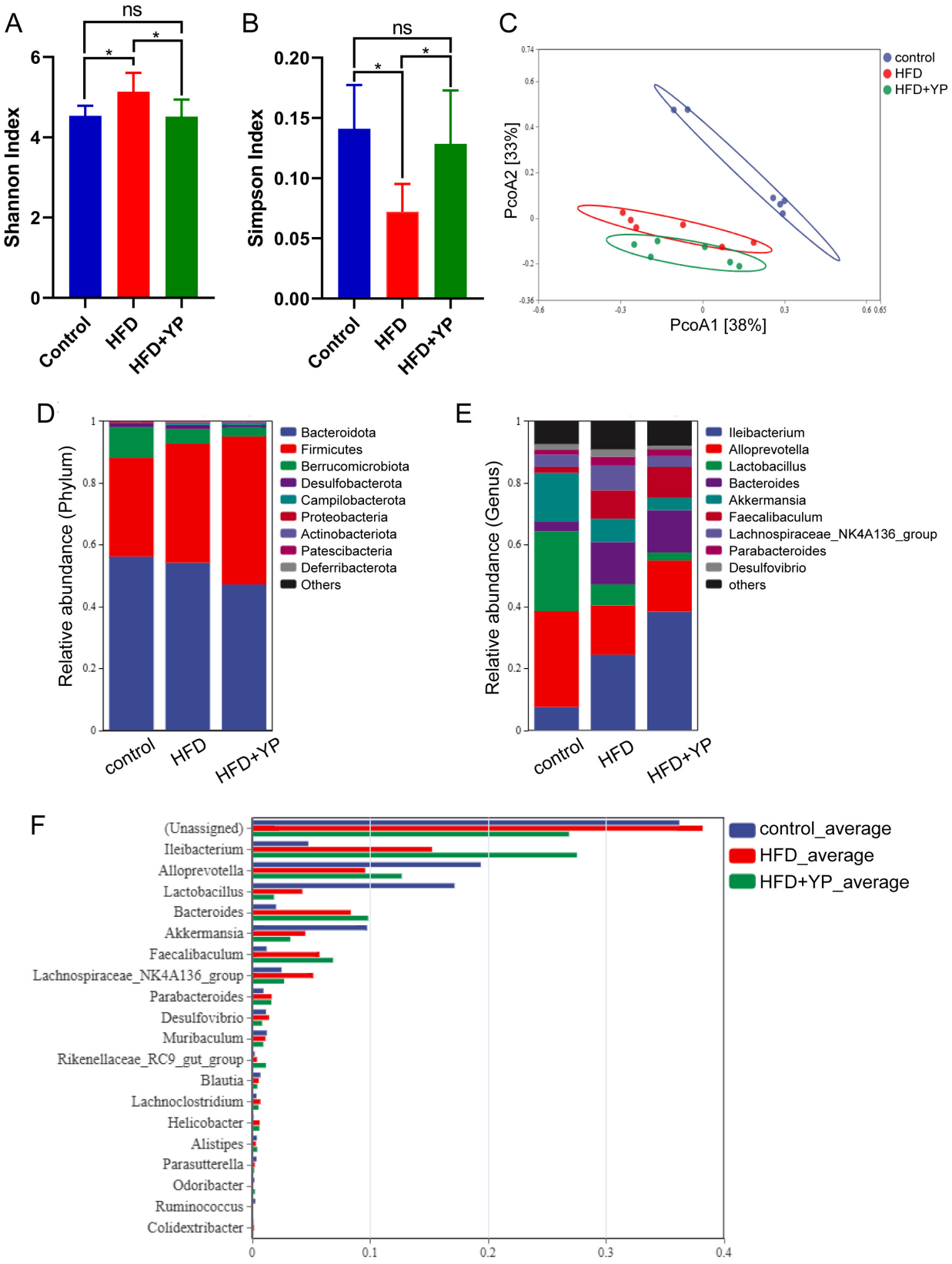

Fig. 3. YP changed the composition of gut microbiota (GM). (A) Shannon index in different groups. (B) Simpson index in different groups. (C) PCoA analysis. (D) Relative abundance of microbial species of the top 10 phyla with significant differences. (E) Relative abundance of microbial species of the top 10 genera with significant differences. (F) Relative abundance of microbial species of the top 20 genera with significant differences. ns, no significance. * $p < 0.05$. PCoA, Principal Coordinates Analysis.

4. Discussion

This study investigated the effects of YP on GM in a GDM mouse model induced by an HFD. Although previous studies have reported the hypoglycemic effects of YP, its potential to improve glucose tolerance by modulating GM has not been explored. In this study, we defined the conventional GDM mouse models, which were typically induced by either HFD or high-fructose intake alone. This refinement is particularly relevant, as modern diets often combine high levels of both fat and fructose-nutritional factors closely linked to obesity, a key contributing factor for GDM [21,22].

In this study, we found that HFD treatment impaired glucose tolerance, establishing a reliable model for GDM. YP demonstrated a significant effect in improving glucose tolerance, likely by enhancing insulin secretion. Furthermore, YP treatment increased the abundance of *Alloprevotella*, while decreasing the abundance of the *Lachnospiraceae NK4A136* group. Growing evidence links systemic inflammation with insulin resistance, a key feature of all types of diabetes, including GDM. An HFD can increase the abundance of lipopolysaccharide (LPS)-producing gut bacteria, which in turn raises blood glucose levels and triggers systemic inflammation [23,24]. Pregnant mice subjected to a high-fructose diet exhibited increased weight gain, elevated fasting glucose, and insulin resistance through the activation of the NF-κB-NLRP3 inflammasome pathway [25]. Based on these findings, we hypothesized that GDM mice induced by HFD exhibit significant inflammation. *Alloprevotella* produces SCFAs, which are key metabolites for maintaining intestinal homeostasis [26,27]. SCFAs have been shown to repair the intestinal epithelial barrier and reduce inflammation [28,29]. Furthermore, *Alloprevotella* is positively correlated with SCFA levels and a decrease in colonic inflammation [30]. In dextran sodium sulfate (DSS)-induced ulcerative colitis (UC) mice, *Alloprevotella* is reduced but increases following treatment [31]. A study has also reported that *Alloprevotella* can improve insulin sensitivity, promote lipolysis, and alleviate obesity [32]. Based on these findings, we speculated that YP may improve glucose tolerance by increasing insulin sensitivity through the augmentation of Alloprevotella abundance.

The *Lachnospiraceae* NK4A136 group was found to be enriched during early pregnancy among women who were later diagnosed with GDM compared with the healthy controls [33]. Additionally, an increased abundance of *Lachnospiraceae* NK4A136 group was observed in a rat model of advanced-stage type 1 diabetes [34]. The *Lachnospiraceae* NK4A136 group was positively correlated with tumor necrosis factor-alpha (TNF-α) [35], which is mainly produced in adipocytes and/or peripheral tissues, and induces tissue-specific inflammation. Elevated levels of TNF-α induce insulin resistance in adipocytes and peripheral tissues by impairing the insulin signaling through serine phosphorylation, ultimately contributing to the development of T2DM [36]. Furthermore, the *Lachnospiraceae* NK4A136 group was significantly positively correlated with at least one systemic inflammation parameter in HFD-induced obese mice [37]. The *Lachnospiraceae* NK4A136 group was also reported to increase in DSS-induced UC mice [38]. Therefore, we inferred that YP could improve inflammation by decreasing the abundance of *Lactobacillus chnospiraceae* NK4A136 group.

The study has several limitations. Firstly, YP administration was evaluated at a single dose, preventing any assessment of potential dose-dependent therapeutic effects on GDM. Secondly, previous research has shown that HFD can induce placental oxidative stress and vascular dysregulation in pregnant mice [39]. For example, Sanches *et al*. [40] reported that HFD feeding led to fetal growth restriction by altering placental thickness and nutrient transport. However, the effects of YP on placental development and fetal growth have not yet been evaluated, and these aspects will be addressed in future studies.

5. Conclusions

YP has the potential to improve glucose intolerance in GDM mice induced by HFD. The regulation of GM is one of the mechanisms underlying the antidiabetic effect of YP in GDM. These findings provide novel insights into the biological activities of YP in the treatment of GDM.

Availability of Data and Materials

The data presented in this study is available from the corresponding author on reasonable request.

Author Contributions

PJ and MH designed the research study. SZ and ZD performed the research. BX, XH and WX analyzed the data. All authors contributed to critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

All animal experiments meet "3Rs" principle. All animal experiments were performed in compliance with the Guide of the Ethics Committee of the First Clinical Medicine School of Guangdong Pharmaceutical University. The ethics approval number is 821015321.

Acknowledgment

We would like to express our gratitude to Dr. De-pei Li from Sun Yat-sen University who helped us during the writing and revising of this manuscript.

Funding

The study was funded by National Natural Science Foundation of China (82104910).

Conflict of Interest

The authors declare no conflict of interest.

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