Integrated Network Pharmacology and Gut Microbiota Study on the Mechanism of Huangqin Decoction in Treatment Diabetic Enteritis

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Objective. Using network pharmacology and gut microbiota sequencing to investigate the probable mechanism of Huangqin decoction in the treatment of Diabetic enteritis (DE). Methods. The mechanism of Huangqin decoction on DE was studied by combining network pharmacology and gut microbiota sequencing analysis. The core components and possible targets of Huangqin decoction were analyzed by network pharmacology. The effect of Huangqin decoction on microorganisms was investigated by gut microbiota sequencing. Results. The results of gut microbiota sequencing analysis showed the abundance of TM7, Tenericutes, Chloroflexi, Cyanobacteria, Acidobacteria, WS6, [Prevotella], Helicobacter, Prevotella, Lactococcus, and Anaeroplasma in the Huangqin decoction group had a significant downward. Using a network pharmacology-related database, 141 main active components of Huangqin decoction were identified, as well as 256 corresponding component targets and 1777 corresponding disease targets; the disease targets and component targets were mapped, and topological analysis was used to determine the potential of Huangqin decoction in the treatment of DE. There were 156 targets, of which the top 20 genes were selected for GO and KEGG. The KEGG results showed that 134 pathways were enriched, which was partially consistent with the metabolic pathways of gut microbiota sequencing analysis. Conclusion. The results show that Huangqin decoction can inhibit the expression of inflammatory factors and related inflammatory pathways in intestinal epithelial cells, thereby regulating the structure of intestinal flora. Using picurst2 for functional prediction and metabolic pathway statistics, seven metabolic pathways were obtained consistent with gut microbiota sequencing, and the NOD-like receptor signaling pathway may be its potential molecular mechanism. These results help to understand the mechanism of Huangqin decoction on DE and provide the theoretical basis for further study of Huangqin decoction.

1. Introduction

Diabetes mellitus is a widespread disease. According to the International Diabetes Federation, it affects 463 million people worldwide with an increasing prevalence [1]. Diabetes is an important public health burden, mainly because of its cardiovascular, renal, and neurological complications. Furthermore, many people with diabetes have upper gastrointestinal (GI) symptoms as well as motor abnormalities. Up to 50% of individuals with type 1 and type 2 diabetes suffer dyspepsia and gastroparesis or are asymptomatic in certain cases, impacting 50% of delayed gastric emptying [2]. These two clinical symptoms share similar pathogenic mechanisms, including autonomic neuropathy, changes in the enteric nervous system, and histological abnormalities. Dyspeptic symptoms are common in people with diabetes, and they are part of the so-called diabetic bowel disease [3]. Studies have shown that the intestinal environment of
T2DM patients is in a chronic low-grade inflammatory response [4]. Some literature has shown that intestinal flora is closely related to the systemic chronic inflammatory response. Oral antibiotics can regulate the intestinal flora of diabetic patients, reduce inflammation in the body, and improve the phenotype of T2DM. It is worth noting that oral antibiotics can inhibit intestinal flora. Antibiotics may also cause damage to the beneficial intestinal flora, leading to an imbalance of intestinal flora, which may have adverse effects on diabetic patients [5].

Huangqin decoction is a traditional Chinese medicine formula in the classic Chinese medical book “Treatise on Febrile Diseases” written by Zhang Zhongjing of the Eastern Han Dynasty. It has a history of nearly 1800 years and is widely used in the clinical treatment of intestinal diseases such as ulcerative colitis [6–9]; it is made by boiling four traditional Chinese medicines: Scutellaria baicalensis, Paeonia lactiflora, jujube, and licorice. In Huangqin decoction, according to traditional Chinese theory, Scutellariae is the king, which is bitter, cold, hardy yin, and clears heat in the interior; Shaoyao is the minister in this medicine, slightly bitter and sour, relieving acute pain, astringing yin, and nourishing. Preserving yin to stop dysentery is essential for treating dysentery; licorice and jujube benefit qi and neutralize the middle. Adjust and supplement the righteousness [10]. Scutellaria baicalensis decoction is precise and has less medicinal flavor. Scutellaria baicalensis has the effect of clearing heat and relieving dysentery, Paeonia lactiflora has the functions of astringing Yin, nourishing and relieving pain, and licorice and jujube can help neutralize the stomach, invigorate the spleen and stop diarrhea, and nourish qi and nourish liquid. On one side, it also has the methods of clearing heat, detoxifying, drying dampness, cooling blood, and nourishing sweetness. Therefore, it is called “the ancestral prescription for treating dysentery.”

Pharmacological studies have shown that Huangqin decoction has anti-inflammatory, antibacterial, analgesic, antipyretic, sedative, and other effects. In recent years, with extensive research on Huangqin decoction, it has been used to treat acute lung injury, colon cancer, gastric cancer, leukemia, and other diseases according to its anti-inflammatory, antiproliferation, and mucosal protective effects [11–14]. It is mainly used to treat intestinal inflammation and is considered to have a significant effect on intestinal inflammation and mucosal protection in the intestinal tract. It was found that intestinal flora played a critical role in the investigation of its mechanism of action [15]. It was discovered that the intestinal flora can not only act directly on the intestinal mucosa, exerting anti-inflammatory and mucosal protective effects, but can also affect the metabolism of the components in Huangqin decoction, metabolizing the more difficult-to-absorb components such as baicalin into the more easily-absorbable components such as baicalein, thereby augmenting the therapeutic effect of Huangqin decoction [7]. Simultaneously, as experimental animal research has progressed and clinical use of Huangqin decoction has expanded, it has been discovered that it has a favorable therapeutic impact in the treatment of ulcerative colitis and other disorders [16].

Therefore, based on network pharmacology and gut microbiota, this study will investigate the mechanism of Huangqin decoction in the treatment of DE.

2. Materials and Methods

2.1. Experimental Materials. Experimental materials are as follows: Scutellaria baicalensis; Baishao; Jujube; Licorice (all purchased from Hebei Quantai Pharmaceutical Co., Ltd.); DNeasy PowerSoil Kit (QIAGEN, Netherlands); Quant-iT PicoGreen dsDNA Assay Kit (Invitrogen, USA); Agcoul AMPure Beads (Beckman Coulter, USA); PicoGreen dsDNA Kit (Invitrogen, USA); CD45 antibody (Santa, USA); PV9004 secondary antibody (Zhongshan, Beijing); DAB chromogen (Zhongshan, Beijing); Quantifluor-ST fluorometer (Promega); high-throughput sequencer (Illumina, USA); low-temperature medical freezer (Haier Co., Ltd.); gdsAUTOS20 gel imaging system (BG Corp., USA); DYY-6C electrophoresis instrument (ABI, USA); paraffin embedding machine (LeicaEG1150H); paraffin microtome (Leica RM 2125 RTS); paraffin microtome (Leica HI1220); and fluorescence microscope (OLYMPUS DP80).

Preparation of Huangqin decoction: weigh the decoction pieces of Radix Scutellariae, Radix Paeoniae Alba, jujube, and licorice in the ratio of 3:2:2:2, add 10 times the total weight of water, soak for 30 minutes, decoc for 1 hour, filter the filtrate, add 8 times the volume of water to decoc for 1 hour, filter the filtrate, combine the two filtrates, and concentrate to 1.5 g/mL, and the low-dose concentration of Huangqin decoction is 0.5 g/mL.

2.2. Experimental Animals. The 48 male db/db mice and 8 db/m mice were purchased from Aiermaite Technology Co., Ltd. (animal certificate number: no. 202009670). The mice were housed in a single cage in a clean-grade barrier system with free food. Drinking water, temperature controlled at 20–26°C, humidity controlled at 40–70% kept 12/12 hours of animal lighting alternating in the light and dark cycle, changing cages, and bedding once a week. All animal experiment-related operations were followed relevant regulations of the Laboratory Animal Ethics Committee of Heilongjiang University of Traditional Chinese Medicine. The db transgenic mice were adaptively fed for one week after purchase, and 2 random blood glucose tests were performed. db/db mice with blood glucose values higher than 11.1 mol/L were selected for grouping and divided into a model group and a low-dose Huangqin decoction group (3.75 g/kg) and Huangqin decoction high-dose group (11.25 g/kg), and db/m mice were the blank group; after grouping, the mice were administered once a day, and the administration volume was 7.5 mg/kg for 8 weeks.

2.3. Sample Collection and Processing. Before the sacrifice, body weights of each mice in tested groups were recorded. After the mice were sacrificed, the cecum contents were taken and placed in a sterile tube in time. After sealing, they were quickly frozen with liquid nitrogen and transferred to a refrigerator at -80°C for storage for subsequent analysis. The epididymal adipose tissue was stored at -75°C. A small
portion of the liver tissue was placed in formaldehyde solution of 4% concentration, and the remaining liver tissue was stored at −80°C for further tests. Similarly, intestinal tissues were collected and frozen for further experimental purposes.

2.4. H&E Staining. The cecal tissues of mice were dehydrated and waxed; slice and paste the cut film on the cover glass to dry; before staining, the para in the section must be removed with xylene, then through high concentration to low concentration alcohol, and finally, into distilled water to dye; put the slices that have been put into distilled water into hematoxylin aqueous solution for dyeing for several minutes; color separation in acid water and ammonia water for several seconds, respectively; after washing with running water for 1 h, add distilled water for a moment; dehydrate in 70% and 90% alcohol for 10 minutes, respectively; add alcohol eosin staining solution for 2~3 minutes.

2.5. Immunohistochemistry. According to the consensus criteria developed for type 1 diabetes, an individual can be diagnosed with insulitis when ≥15 CD45+ cells are found within the parenchyma or in the islet-exocrine interface in ≥3 islets. The changes of expression of CD45 in the cecal tissue of diabetic cardiomyopathy mice were taken from the cecum tissues, fixed with wax blocks, and then, cut and sealed for 78 degrees in the oven. After the morning was taken out, the xylene was fixed for 10 min, dehydrated with alcohol, then dehydrated 5~10 min; distilled water was washed for 2 times, 3~5 min/times, 3% H2O2 blocked 10 min; distilled water was cleaned 2 times, 3~5 min/times. Citric acid repair (add the tissue after boiling water, stop heating after steam, open the air valve after 2~3 minutes, open the cover after 7 minutes, and take out the tissue), cool for about 50 minutes, wash the tissue with PBS for 3 times after cooling, 5 min/time, and add primary antibody (100 μg 50). Incubate overnight at 4°C, wash PBS for 3 times the next day, 5 min/time, and add secondary antibody (100 μg 50). Incubate at room temperature for 30 min, wash with PBS for 3 times, 5 min/time, DAB color development for 5-10 minutes (block the color development after observing the color development under the microscope), hematoxylin reappears for 1 min after washing with water for 3-5 minutes, wash with water for 10-15 minutes after observing the dyeing degree under the microscope (if it is not ideal, it can be dyed repeatedly), dehydrate and dealclohalic for 2-3 min/time after washing with distilled water, and finally, seal the neutral gum in the incubator at 87°C for 2-3 days. The film is taken under the microscope and stored in the computer.

2.6. 16S rRNA Gene Sequencing

2.6.1. DNA Extraction from Stool Samples. The Dneasy powerOil kit of QIAGEN company was used for extraction and DNA detection. The absorbance values of the extracted DNA were measured at 260 nm and 280 nm, respectively, by fluorescence spectrophotometer, the concentration of DNA was calculated, and the quality of DNA was detected by agarose gel electrophoresis of 1%. Adjust the concentration of DNA solution according to the results, and then, store the
adjusted DNA working solution in a 4°C refrigerator and the storage solution in a -20°C refrigerator.

2.6.2. 16S rRNA Gene Amplicon Sequencing. The v3-v4 region of the 16S rRNA gene of flora was amplified by PCR with forward primer (ACTCCTACGGGAGGCAGC A) and reverse primer (GGACTACHVGGGTWTCTAAAT). The sample-specific 7bp barcode was integrated into primers for multiple sequencing. The PCR component contains 5 μL Q5 reaction buffer (5) ×, 5 μL Q5 high fidelity GC

| Group                  | Chao1   | Faith_pd | Goods_coverage | Observed_species | Pielou_e | Shannon | Simpson |
|------------------------|---------|----------|----------------|------------------|----------|---------|---------|
| Control group          | 2012.334| 94.2689  | 0.9889872      | 1731.78          | 0.7317398| 7.82702 | 0.9813612|
| Model group            | 1875.298| 88.86688 | 0.9886164      | 1586.6           | 0.7124886| 7.56511 | 0.9707218|
| Huangqin decoction group| 1921.75 | 91.23156 | 0.989444       | 1669.04          | 0.7156288| 7.692342| 0.97627  |

Figure 3: (a) Venn diagram of OTUs of gut microbiota in each group (K is blank group; M is model group; Q is Huangqin decoction group); (b–d) sparse curve of the intestinal flora of rat samples in each group (b), species accumulation curve (c), and rank-abundance curve (d).
Figure 4: Abundance distribution of intestinal flora in each group of rat samples at phylum (a) and genus (b) levels; analysis of the distribution of bacterial community structure in each group of rat samples (c).
GeneCards database was used to search the relevant target of traditional Chinese medicine. The database, and the gene name was transformed to obtain was obtained, which was imported into the Uniprot database (http://www.uniprot.org/). The target information and protein names were standardized using the Uniprot database, the active components of Huangqin decoction and DE utilization (OB).

Screened components were supplemented in combination with literature reports. The obtained components were screened under the conditions of oral absorption and utilization (OB).

Network Pharmacology Analysis. The Cytoscape v3.8.2 software was used to visualize and analyze the protein interaction analysis results of the STRING database to construct a protein-protein interaction network. The clusterProfiler package in R language was used to perform GO functional annotation enrichment analysis and KEGG pathway analysis for common targets. The enriched pathways are the potential pathways for the drug to play a therapeutic role, and a histogram is drawn to visualize it.

Table 2: Statistical chart of difference analysis between groups.

| Group 1 | Group 2 | Sample size | Permutations | PseudoF | P value | q value |
|---------|---------|-------------|--------------|----------|---------|---------|
| All     | —       | 15          | 999          | 2.935413 | 0.001   | —       |
| K       | M       | 10          | 999          | 2.408184 | 0.011   | 0.012   |
| K       | Q       | 10          | 999          | 3.450399 | 0.011   | 0.012   |
| M       | Q       | 10          | 999          | 2.986695 | 0.012   | 0.012   |

3. Results

3.1. H&E Staining. The degree of damage to the integrity of the intestinal barrier reflects the barrier function of the intestinal mucosa to a certain extent. In this study, the length of the intestinal mucosal villi and the thickness of the muscular layer were observed by H&E staining to determine the change of the intestinal mucosal barrier function, as shown in Figure 1. H&E staining showed that the villus length and muscle thickness of the intestinal mucosa in the blank group were normal (Figure 1(a)); the villi were shortened, and the muscle layer thickness was decreased in the model group (Figure 1(b)); the symptoms of the Huangqin decoction group were more severe than those of the model group. The villus length was similar to that of the blank group, but the thickness of the muscle layer was still significantly lower than that of the blank group (Figure 1(c)).

3.2. Immunohistochemistry. The intestinal mucosa was sectioned, and the differences in leukocyte infiltration were observed by CD45 staining, as shown in Figure 2. In the blank group, only a few CD45+ cells were infiltrated. Compared with the blank group, the infiltration of CD45+ cells in the model group were significantly increased, while that in the Huangqin decoction group was significantly less than that in the model group (Figures 2(a)–2(c)).

3.3. 16S rRNA Gene Sequencing

3.3.1. Classification and Analysis of OTUs (Operational Taxonomic Units) of Gut Microbiota in Samples from Each Group. The blank group has a total of 5450 OTUs and 3297 unique OTUs, the model group has a total of 5678 OTUs and 3561 unique OTUs, the Scutellaria baicalensis group has a total of 5580 OTUs and 3747 unique OTUs, and the three groups have a total of 837 OTUs, as shown in Figure 3. Compared with the blank group, the number of OTUs in the model group was significantly increased; compared with the model group, the number of OTUs in the administration group was significantly downregulated.
Figure 5: Random forest plot of differential gut microbiota of samples in each group. Note: (a) phylum-level differential gut microbiota; (b) class-level differential gut microbiota; (c) order-level differential gut microbiota; (d) family-level differential gut microbiota; (e) genus-level differential gut microbiota; (f) species-level differential gut microbiota.
### Table 3: Signal pathway of DE.

| Pathway       | Description                                           |
|---------------|-------------------------------------------------------|
| ko00010       | Glycolysis/gluconeogenesis                             |
| ko00020       | Citrate cycle (TCA cycle)                              |
| ko00030       | Pentose phosphate pathway                              |
| ko00040       | Pentose and glucuronate interconversions               |
| ko00051       | Fructose and mannose metabolism                        |
| ko00052       | Galactose metabolism                                   |
| ko00053       | Ascorbate and aldarate metabolism                      |
| ko00061       | Fatty acid biosynthesis                                |
| ko00071       | Fatty acid metabolism                                  |
| ko00072       | Synthesis and degradation of ketone bodies             |
| ko00100       | Steroid biosynthesis                                   |
| ko00120       | Primary bile acid biosynthesis                         |
| ko00121       | Secondary bile acid biosynthesis                       |
| ko00130       | Ubiquinone and other terpenoid-quinone biosynthesis    |
| ko00140       | Steroid hormone biosynthesis                           |
| ko00190       | Oxidative phosphorylation                              |
| ko00195       | Photosynthesis                                         |
| ko00196       | Photosynthesis-antenna proteins                        |
| ko00230       | Purine metabolism                                      |
| ko00240       | Pyrimidine metabolism                                  |
| ko00250       | Alanine, aspartate, and glutamate metabolism           |
| ko00253       | Tetracycline biosynthesis                              |
| ko00260       | Glycine, serine, and threonine metabolism              |
| ko00270       | Cysteine and methionine metabolism                     |
| ko00280       | Valine, leucine, and isoleucine degradation            |
| ko00281       | Geraniol degradation                                   |
| ko00290       | Valine, leucine, and isoleucine biosynthesis           |
| ko00300       | Lysine biosynthesis                                    |
| ko00310       | Lysine degradation                                     |
| ko00311       | Penicillin and cephalosporin biosynthesis              |
| ko00312       | Beta-lactam resistance                                 |
| ko00330       | Arginine and proline metabolism                        |
| ko00340       | Histidine metabolism                                   |
| ko00350       | Tyrosine metabolism                                    |
| ko00360       | Phenylalanine metabolism                               |
| ko00361       | Chlorocyclohexane and chlorobenzene degradation        |
| ko00362       | Benzoate degradation                                   |
| ko00363       | Bisphenol degradation                                  |
| ko00364       | Fluorobenzoate degradation                             |
| ko00380       | Tryptophan metabolism                                  |
| ko00400       | Phenylalanine, tyrosine, and tryptophan biosynthesis   |
| ko00410       | Beta-alanine metabolism                                |
| ko00430       | Taurine and hypotaurine metabolism                     |
| ko00440       | Phosphonate and phosphinate metabolism                 |
| ko00450       | Selenocompound metabolism                              |
| ko00460       | Cyanooamino acid metabolism                            |
| ko00471       | D-glutamine and D-glutamate metabolism                 |
| ko00472       | D-arginine and D-ornithine metabolism                  |
| Pathway      | Description                                      |
|--------------|--------------------------------------------------|
| ko00473      | D-alanine metabolism                             |
| ko00480      | Glutathione metabolism                           |
| ko00500      | Starch and sucrose metabolism                    |
| ko00510      | N-glycan biosynthesis                            |
| ko00511      | Other glycan degradation                          |
| ko00520      | Amino sugar and nucleotide sugar metabolism      |
| ko00521      | Streptomyycin biosynthesis                        |
| ko00523      | Polypeptide sugar unit biosynthesis               |
| ko00524      | Butirosin and neomycin biosynthesis              |
| ko00531      | Glycosaminoglycan degradation                     |
| ko00540      | Lipopolysaccharide biosynthesis                   |
| ko00550      | Peptidoglycan biosynthesis                        |
| ko00561      | Glycerolipid metabolism                           |
| ko00562      | Inositol phosphate metabolism                     |
| ko00564      | Glycerophospholipid metabolism                    |
| ko00590      | Arachidonic acid metabolism                       |
| ko00591      | Linoleic acid metabolism                          |
| ko00600      | Sphingolipid metabolism                           |
| ko00601      | Glycosphingolipid biosynthesis-lacto and neolacto series |
| ko00620      | Pyruvate metabolism                              |
| ko00621      | Dioxin degradation                                |
| ko00622      | Xylene degradation                                |
| ko00623      | Toluene degradation                               |
| ko00624      | Polycyclic aromatic hydrocarbon degradation       |
| ko00625      | Chloroalkane and chloroalkene degradation         |
| ko00627      | Aminobenzoate degradation                         |
| ko00630      | Glyoxylate and dicarboxylate metabolism           |
| ko00633      | Nitrotoluene degradation                          |
| ko00640      | Propanoate metabolism                             |
| ko00642      | Ethylbenzene degradation                          |
| ko00643      | Styrene degradation                               |
| ko00650      | Butanoate metabolism                              |
| ko00660      | C5-branched dibasic acid metabolism               |
| ko00670      | One carbon pool by folate                         |
| ko00680      | Methane metabolism                                |
| ko00710      | Carbon fixation in photosynthetic organisms       |
| ko00720      | Carbon fixation pathways in prokaryotes           |
| ko00730      | Thiamine metabolism                               |
| ko00740      | Riboflavin metabolism                             |
| ko00750      | Vitamin B6 metabolism                             |
| ko00760      | Nicotinate and nicotinamide metabolism            |
| ko00770      | Pantothenate and CoA biosynthesis                 |
| ko00780      | Biotin metabolism                                 |
| ko00785      | Lipoic acid metabolism                            |
| ko00790      | Folate biosynthesis                               |
| ko00791      | Atrazine degradation                              |
| ko00830      | Retinol metabolism                                |
| ko00860      | Porphyrin and chlorophyll metabolism              |
| Pathway | Description |
|---------|-------------|
| ko00900 | Terpenoid backbone biosynthesis |
| ko00903 | Limonene and pinene degradation |
| ko00906 | Carotenoid biosynthesis |
| ko00908 | Zeatin biosynthesis |
| ko00909 | Sesquiterpenoid biosynthesis |
| ko00910 | Nitrogen metabolism |
| ko00920 | Sulfur metabolism |
| ko00930 | Caprolactam degradation |
| ko00941 | Flavonoid biosynthesis |
| ko00943 | Isoflavonoid biosynthesis |
| ko00960 | Tropane, piperidine, and pyridine alkaloid biosynthesis |
| ko00965 | Betalain biosynthesis |
| ko00970 | Aminoacyl-tRNA biosynthesis |
| ko00980 | Metabolism of xenobiotics by cytochrome P450 |
| ko00983 | Drug metabolism-other enzymes |
| ko01040 | Biosynthesis of unsaturated fatty acids |
| ko01051 | Biosynthesis of ansamycins |
| ko01053 | Biosynthesis of siderophore group nonribosomal peptides |
| ko01055 | Biosynthesis of vancomycin group antibiotics |
| ko01056 | Biosynthesis of type II polyketide backbone |
| ko02010 | ABC transporters |
| ko02020 | Two-component system |
| ko02030 | Bacterial chemotaxis |
| ko02040 | Flagellar assembly |
| ko02060 | Phosphotransferase system (PTS) |
| ko03008 | Ribosome biogenesis in eukaryotes |
| ko03010 | Ribosome |
| ko03013 | RNA transport |
| ko03015 | mRNA surveillance pathway |
| ko03018 | RNA degradation |
| ko03020 | RNA polymerase |
| ko03030 | DNA replication |
| ko03040 | Spliceosome |
| ko03050 | Proteasome |
| ko03060 | Protein export |
| ko03070 | Bacterial secretion system |
| ko03410 | Base excision repair |
| ko03420 | Nucleotide excision repair |
| ko03430 | Mismatch repair |
| ko03440 | Homologous recombination |
| ko03450 | Nonhomologous end-joining |
| ko04020 | Calcium signaling pathway |
| ko04112 | Cell cycle-Caulobacter |
| ko04113 | Meiosis-yeast |
| ko04122 | Sulfur relay system |
| ko04141 | Protein processing in endoplasmic reticulum |
| ko04142 | Lysosome |
| ko04144 | Endocytosis |
3.3.2. Alpha Diversity Analysis of Gut Microbiota in Each Group. As shown in Figures 3(b)–3(d), the diversity of samples in each group is almost saturated, indicating that the sequencing depth is sufficient and the sample size of each group is sufficient to reflect the richness of the community. The biodiversity indexes of the three groups of samples were compared, as shown in Table 1. Compared with the blank group, the intestinal flora Chao1, Faith_pd, Goods_coverage, Observed_species, Pioulou_e, Shannon, and Simpson indexes of mice in the model group all showed a downward trend. After the administration of Huangqin decoction, all diversity indices showed a downward trend, as shown in Table 1.

3.3.3. Taxonomic Composition Analysis of Gut Microbiota in Each Group. Through the analysis of Figures 4(a) and 4(b), it is found that Bacteroides and Firmicutes are the most important phyla at the phylum level, followed by tenericetes, Proteobacteria, and actinobacteria. These five phyla account for a very high proportion of the whole phyla and belong to the dominant phyla. Compared with the blank group, in the model group, bacteroidea (54.25% → 43.77%), Firmicutes (38.06% → 47.37%), Proteus (2.98% → 0.01%), actinomycetes (0.89% → 0.73%), and Firmicutes/Bacteroidetes ratio in the blank group was 0.70, and Firmicutes/Bacteroidetes ratio in the model group was 1.08. It is suggested that the dominant flora of model group mice and blank group mice has changed significantly in the structure; compared with the model group, the ratio of Firmicutes/Bacteroidetes in Huangqin decoction group was 1.14, suggesting that Huangqin decoction could regulate the dominant flora of db/db mice.

3.3.4. Influence of Gut Microbiota on Beta Diversity Analysis. In this study, PCoA analysis was used to investigate the differences in the beta diversity of rat gut microbiota. There was no significant difference in the diversity of bacterial community structure in the blank, model, and Huangqin decoction groups, and the communities in each group fell within their respective ranges, with strong similarity. The results showed that compared with the blank group, the microflora of the mice in the model group were significantly

| Pathway          | Description                                      |
|------------------|--------------------------------------------------|
| ko04145          | Phagosome                                        |
| ko04146          | Peroxisome                                       |
| ko04210          | Apoptosis                                        |
| ko04310          | Wnt signaling pathway                            |
| ko04621          | NOD-like receptor signaling pathway              |
| ko04622          | RIG-I-like receptor signaling pathway            |
| ko04626          | Plant-pathogen interaction                       |
| ko04722          | Neurotrophin signaling pathway                   |
| ko04910          | Insulin signaling pathway                        |
| ko04962          | Vasopressin-regulated water reabsorption         |
| ko04974          | Protein digestion and absorption                 |
| ko05010          | Alzheimer’s disease                               |
| ko05012          | Parkinson’s disease                               |
| ko05100          | Bacterial invasion of epithelial cells           |
| ko05110          | Vibrio cholerae infection                        |
| ko05111          | Vibrio cholerae pathogenic cycle                 |
| ko05120          | Epithelial cell signaling in Helicobacter pylori infection |
| ko05130          | Pathogenic Escherichia coli infection            |
| ko05131          | Shigellois                                       |
| ko05143          | African trypanosomiasis                          |
| ko05145          | Toxoplasmosis                                    |
| ko05146          | Amoebiasis                                       |
| ko05150          | Staphylococcus aureus infection                  |
| ko05200          | Pathways in cancer                               |
| ko05322          | Systemic lupus erythematosus                     |
| ko05410          | Hypertrophic cardiomyopathy (HCM)                |

Table 3: Continued.
### Table 4: Effective ingredients of HQD.

| MOL ID      | Ingredient                  | OB (%)  | DL     | Source                                           |
|-------------|-----------------------------|---------|--------|-------------------------------------------------|
| MOL000422   | Kaempferol                  | 41.8822 | 0.2406 | Licorice, white peony root                       |
| MOL000359   | Sitosterol                  | 36.9139 | 0.7512 | Licorice, Scutellaria baicalensis, white peony root |
| MOL000098   | Quercetin                   | 46.4334 | 0.2752 | Jujube, licorice                                |
| MOL000211   | Mairin                      | 55.3770 | 0.7761 | Jujube, licorice, white peony root               |
| MOL000358   | Beta-sitosterol             | 36.9139 | 0.7512 | Jujube, Scutellaria baicalensis, white peony root |
| MOL000449   | Stigmasterol                | 43.8298 | 0.7566 | Jujube, Scutellaria baicalensis                  |
| MOL000492   | (+)-catechin                | 54.8264 | 0.2416 | Jujube, white peony root                         |
| MOL000096   | (−)-catechin                | 49.6763 | 0.2416 | Jujube                                          |
| MOL000627   | Stepholidine                | 33.1062 | 0.5408 |                                                |
| MOL000787   | Fumarine                    | 59.2625 | 0.8269 |                                                |
| MOL001454   | Berberine                   | 36.8612 | 0.7766 |                                                |
| MOL001522   | S-coclaurine                | 42.3506 | 0.2351 |                                                |
| MOL002773   | Beta-carotene               | 37.1843 | 0.5835 |                                                |
| MOL004350   | (+)-catechin                | 54.8264 | 0.2416 |                                                |
| MOL000096   | (−)-catechin                | 49.6763 | 0.2416 |                                                |
| MOL000627   | Stepholidine                | 33.1062 | 0.5408 |                                                |
| MOL000787   | Fumarine                    | 59.2625 | 0.8269 |                                                |
| MOL001454   | Berberine                   | 36.8612 | 0.7766 |                                                |
| MOL001522   | S-coclaurine                | 42.3506 | 0.2351 |                                                |
| MOL002773   | Beta-carotene               | 37.1843 | 0.5835 |                                                |
| MOL004350   | (+)-catechin                | 54.8264 | 0.2416 |                                                |
| MOL000096   | (−)-catechin                | 49.6763 | 0.2416 |                                                |
| MOL000627   | Stepholidine                | 33.1062 | 0.5408 |                                                |
| MOL000787   | Fumarine                    | 59.2625 | 0.8269 |                                                |
| MOL001454   | Berberine                   | 36.8612 | 0.7766 |                                                |
| MOL001522   | S-coclaurine                | 42.3506 | 0.2351 |                                                |
| MOL002773   | Beta-carotene               | 37.1843 | 0.5835 |                                                |
| MOL004350   | (+)-catechin                | 54.8264 | 0.2416 |                                                |
| MOL000096   | (−)-catechin                | 49.6763 | 0.2416 |                                                |
| MOL000627   | Stepholidine                | 33.1062 | 0.5408 |                                                |
| MOL000787   | Fumarine                    | 59.2625 | 0.8269 |                                                |
| MOL001454   | Berberine                   | 36.8612 | 0.7766 |                                                |
| MOL001522   | S-coclaurine                | 42.3506 | 0.2351 |                                                |
| MOL002773   | Beta-carotene               | 37.1843 | 0.5835 |                                                |
| MOL004350   | (+)-catechin                | 54.8264 | 0.2416 |                                                |
| MOL000096   | (−)-catechin                | 49.6763 | 0.2416 |                                                |
| MOL000627   | Stepholidine                | 33.1062 | 0.5408 |                                                |
| MOL000787   | Fumarine                    | 59.2625 | 0.8269 |                                                |
| MOL001454   | Berberine                   | 36.8612 | 0.7766 |                                                |
| MOL001522   | S-coclaurine                | 42.3506 | 0.2351 |                                                |
| MOL002773   | Beta-carotene               | 37.1843 | 0.5835 |                                                |
| MOL004350   | (+)-catechin                | 54.8264 | 0.2416 |                                                |
| MOL000096   | (−)-catechin                | 49.6763 | 0.2416 |                                                |
| MOL000627   | Stepholidine                | 33.1062 | 0.5408 |                                                |
| MOL000787   | Fumarine                    | 59.2625 | 0.8269 |                                                |
| MOL001454   | Berberine                   | 36.8612 | 0.7766 |                                                |
| MOL001522   | S-coclaurine                | 42.3506 | 0.2351 |                                                |
| MOL002773   | Beta-carotene               | 37.1843 | 0.5835 |                                                |
| MOL004350   | (+)-catechin                | 54.8264 | 0.2416 |                                                |
| MOL000096   | (−)-catechin                | 49.6763 | 0.2416 |                                                |
| MOL000627   | Stepholidine                | 33.1062 | 0.5408 |                                                |
| MOL000787   | Fumarine                    | 59.2625 | 0.8269 |                                                |
| MOL001454   | Berberine                   | 36.8612 | 0.7766 |                                                |
| MOL001522   | S-coclaurine                | 42.3506 | 0.2351 |                                                |
| MOL002773   | Beta-carotene               | 37.1843 | 0.5835 |                                                |
| MOL004350   | (+)-catechin                | 54.8264 | 0.2416 |                                                |
| MOL000096   | (−)-catechin                | 49.6763 | 0.2416 |                                                |
| MOL000627   | Stepholidine                | 33.1062 | 0.5408 |                                                |
| MOL000787   | Fumarine                    | 59.2625 | 0.8269 |                                                |
| MOL001454   | Berberine                   | 36.8612 | 0.7766 |                                                |
| MOL001522   | S-coclaurine                | 42.3506 | 0.2351 |                                                |
| MOL002773   | Beta-carotene               | 37.1843 | 0.5835 |                                                |
| MOL004350   | (+)-catechin                | 54.8264 | 0.2416 |                                                |
| MOL000096   | (−)-catechin                | 49.6763 | 0.2416 |                                                |
| MOL000627   | Stepholidine                | 33.1062 | 0.5408 |                                                |
| MOL000787   | Fumarine                    | 59.2625 | 0.8269 |                                                |
| MOL001454   | Berberine                   | 36.8612 | 0.7766 |                                                |
| MOL001522   | S-coclaurine                | 42.3506 | 0.2351 |                                                |
| MOL002773   | Beta-carotene               | 37.1843 | 0.5835 |                                                |
| MOL004350   | (+)-catechin                | 54.8264 | 0.2416 |                                                |
| MOL000096   | (−)-catechin                | 49.6763 | 0.2416 |                                                |
| MOL000627   | Stepholidine                | 33.1062 | 0.5408 |                                                |
| MOL000787   | Fumarine                    | 59.2625 | 0.8269 |                                                |
| MOL001454   | Berberine                   | 36.8612 | 0.7766 |                                                |
| MOL001522   | S-coclaurine                | 42.3506 | 0.2351 |                                                |
| MOL002773   | Beta-carotene               | 37.1843 | 0.5835 |                                                |
| MOL004350   | (+)-catechin                | 54.8264 | 0.2416 |                                                |
| MOL ID   | Ingredient                                      | OB (%)  | DL     | Source |
|----------|-------------------------------------------------|---------|--------|--------|
| MOL004959 | 1-Methoxyphaseollidin                           | 36.56537233 | 0.32291 |        |
| MOL004966 | 3′-Hydroxy-4′-O-methylglabridin                  | 43.71495141 | 0.57406 |        |
| MOL004974 | 3′-Methoxyglabridin                             | 46.16150929 | 0.57393 |        |
| MOL005000 | Gancaonin G                                     | 60.43520506 | 0.39404 |        |
| MOL005001 | Gancaonin H                                     | 50.10372327 | 0.78416 |        |
| MOL005007 | Glyasperins M                                   | 72.67080984 | 0.59274 |        |
| MOL005008 | Glycyrrhiza flavonol A                         | 41.27527733 | 0.59512 |        |
| MOL000497 | Licochalcone a                                  | 40.78965199 | 0.28517 |        |
| MOL004328 | Naringenin                                      | 37.65518912 | 0.20935 |        |
| MOL004903 | Liquiritin                                      | 65.69011165 | 0.73893 |        |
| MOL000392 | Formononetin                                    | 69.67388061 | 0.21202 |        |
| MOL000500 | Jaranol                                         | 50.82881677 | 0.29148 |        |
| MOL001792 | DFV                                             | 32.7627375 | 0.18316 |        |
| MOL002565 | Medicarpin                                      | 49.21981761 | 0.3351  |        |
| MOL003896 | 7-Methoxy-2-methyl isoflavone                  | 42.56474148 | 0.19946 |        |
| MOL004835 | Glypallichalcone                                | 61.59706227 | 0.18993 |        |
| MOL004941 | (2R)-7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one| 41.27527733 | 0.59512 |        |
| MOL004957 | HMO                                             | 38.3654238 | 0.21067 |        |
| MOL004978 | 2-[(3R)-8,8-dimethyl-3,4-dihydro-2H-pyrano[6,5-f]chromen-3-yl]-5-methoxyphenol | 36.21429208 | 0.52122 |        |
| MOL000239 | Jaranol                                         | 50.82881677 | 0.29148 |        |
| MOL001484 | Inermine                                        | 75.18306038 | 0.53754 |        |
| MOL004806 | Euchrenone                                      | 30.28726099 | 0.57386 |        |
| MOL004815 | (E)-1-(2,4-dihydroxyphenyl)-3-(2,2-dimethylchromen-6-yl)prop-2-en-1-one | 39.61685537 | 0.35077 |        |
| MOL004833 | Phaseolinosiflavan                              | 32.00810772 | 0.44538 |        |
| MOL004866 | 2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-6-(3-methylbut-2-enyl)chromone | 44.15196126 | 0.41482 |        |
| MOL004891 | Shintterocarpin                                 | 80.29527688 | 0.72746 |        |
| MOL004908 | Glabridin                                       | 53.24514328 | 0.46967 |        |
| MOL004910 | Glabranin                                       | 52.89565508 | 0.31208 |        |
| MOL004911 | Glabrene                                        | 46.26685721 | 0.43902 |        |
| MOL004912 | Glabrone                                        | 52.51217419 | 0.49645 |        |
| MOL004915 | Euryrcarpin A                                   | 43.27728425 | 0.37429 |        |
| MOL004945 | (2S)-7-hydroxy-2-(4-hydroxyphenyl)-8-(3-methylbut-2-enyl)chroman-4-one | 36.56537233 | 0.32291 |        |
| MOL004961 | Quercetin der.                                  | 46.4493884 | 0.3343  |        |
| MOL004980 | Inlacoumarin A                                  | 39.70909598 | 0.32613 |        |
| MOL004989 | 6-Prenylated eriodictyol                       | 39.22383018 | 0.41259 |        |
| MOL004991 | 7-Acetoxy-2-methylisoflavone                   | 38.92333105 | 0.26217 |        |
| MOL004993 | 8-Prenylated eriodictyol                       | 53.79476318 | 0.40383 |        |
| MOL005003 | Licoagrocarpin                                  | 58.81390287 | 0.58498 |        |
| MOL005012 | Licoagroisoflavone                             | 57.28224098 | 0.48679 |        |
| MOL005016 | Odoratin                                        | 49.9482187 | 0.30487 |        |
| MOL005020 | Dehydroglyasperins C                           | 53.82326014 | 0.37006 |        |
| MOL000417 | Calycosin                                       | 47.75182783 | 0.24278 |        |
| MOL004838 | 8-(6-Hydroxy-2-benzofuranyl)-2,2-dimethyl-5-chromenol | 58.43728091 | 0.38106 |        |
| MOL004863 | 3-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-8-(3-methylbut-2-enyl)chromone | 66.37125046 | 0.41392 |        |
| MOL ID   | Ingredient                                                                 | OB (%) | DL    | Source     |
|----------|----------------------------------------------------------------------------|--------|-------|------------|
| MOL002311 | Glycyrol                                                                  | 90.77578223 | 0.66819 |
| MOL004805 | (2S)-2-[4-hydroxy-3-(3-methylbut-2-yl)phenyl]-8,8-dimethyl-2,3-dihydropyrano[2,3-f]chromen-4-one | 31.78703353 | 0.72403 |
| MOL004814 | Isotrifoliol                                                               | 31.94478724 | 0.42422 |
| MOL004841 | Licochalcone B                                                             | 76.75735485 | 0.1935  |
| MOL004848 | Licochalcone G                                                             | 49.25496332 | 0.32325 |
| MOL004898 | (E)-3-[3,4-dihydroxy-5-(3-methylbut-2-yl)phenyl]-1-(2,4-dihydroxyphenyl)prop-2-en-1-one | 46.26792256 | 0.3062  |
| MOL004907 | Glyzaglabrin                                                               | 61.06886361 | 0.35347 |
| MOL004924 | (-)-Medicocarpin                                                           | 40.99397199 | 0.95059 |
| MOL004935 | Sigmoidin-B                                                                | 34.88108616 | 0.41455 |
| MOL004948 | Isolicoflavonol                                                            | 45.16990058 | 0.41859 |
| MOL004985 | Icos-5-enoic acid                                                          | 30.70294255 | 0.19725 |
| MOL004990 | 7,2',4'-trihydroxy-5-methoxy-3-arylcoumarin                               | 83.71436744 | 0.27136 |
| MOL005017 | Phaseol                                                                    | 78.76621925 | 0.57867 |
| MOL005018 | Xambioona                                                                  | 54.84916242 | 0.87419 |
| MOL005013 | 1,3-Dihydroxy-9-methoxy-6-benzofuran[3,2-c]chromenone                      | 48.14154235 | 0.48231 |
| MOL005014 | 1,3-Dihydroxy-8,9-methoxy-6-benzofuran[3,2-c]chromenone                   | 62.90135486 | 0.52759 |
| MOL004985 | Icos-5-enoic acid                                                          | 30.70294255 | 0.19725 |
| MOL004996 | Gadeldiacid acid                                                           | 30.70294255 | 0.19725 |
| MOL004882 | Licoquimaron                                                                 | 33.21085068 | 0.3568  |
| MOL001789 | Isoliquiritigenin                                                          | 85.32    | 0.15   |
| MOL004804 | 18Beta-glycyrrhetinic acid                                                 | 22.05    | 0.74   |
| MOL000073 | Ent-epicatechin                                                             | 48.95984114 | 0.24162 |
| MOL000173 | Wogonin                                                                    | 30.68456706 | 0.22942 |
| MOL000228 | (2R)-7-hydroxy-5-methoxy-2-phenylchroman-4-one                             | 55.23317389 | 0.20163 |
| MOL000525 | Norwogonin                                                                 | 39.40397184 | 0.20723 |
| MOL000552 | 5,2'-Dihydroxy-6,7,8-trimethoxyflavone                                     | 31.71246493 | 0.35462 |
| MOL001458 | Coptisine                                                                   | 30.671852  | 0.85647 |
| MOL001490 | Bis[(2S)-2-ethylhexyl] benzene-1,2-dicarboxylate                           | 43.59332547 | 0.34531 |
| MOL001689 | Acacetin                                                                    | 34.97357273 | 0.24082 |
| MOL002714 | Baicalein                                                                   | 33.51891869 | 0.24082 |
| MOL002879 | Diop                                                                        | 43.59332547 | 0.39247 |
| MOL002897 | Epiberberine                                                               | 43.09233228 | 0.7761  |
| MOL002909 | 5,7,2,5-Tetrahydroxy-8,6-dimethoxyflavone                                 | 33.81582599 | 0.44739 |
| MOL002910 | Carthaminid                                                                 | 41.15096273 | 0.24189 |
| MOL002913 | Dihydrobaicalcin qt                                                        | 40.03778103 | 0.20722 |
| MOL002914 | Eriodictyiol (flavanone)                                                   | 41.35042713 | 0.2436  |
| MOL002915 | Salvigenin                                                                  | 49.06592606 | 0.33279 |
| MOL002917 | 5,2',6'-Trihydroxy-7,8-dimethoxyflavone                                   | 45.04742802 | 0.33057 |
| MOL002925 | 5,7,2',6'-Tetrahydroxyflavone                                             | 37.01348688 | 0.24382 |
| MOL002927 | Skullcapflavone II                                                         | 69.51043398 | 0.4379  |
| MOL002928 | Oroxylin a                                                                  | 41.367569   | 0.23323 |
| MOL002932 | Panicolin                                                                   | 76.25704989 | 0.2915  |
| MOL002933 | 5,7,4'-Trihydroxy-8-methoxyflavone                                         | 36.56200469 | 0.26666 |
| MOL002934 | Neobaicaline                                                               | 104.3446052 | 0.43917 |
| MOL002937 | Dihydrooroxylin                                                           | 66.06173872 | 0.23057 |

Table 4: Continued.
separated, indicating that the beta diversity of the two groups was significantly different. After administration of Huangqin decoction, it tended to the blank group, indicating that the beta diversity of the Huangqin decoction group was similar to that of the normal group. After administration of Huangqin decoction, it had a certain effect on the body of DE mice, as shown in Figure 4(c).

Differences between groups were analyzed by (permutational multivariate analysis of variance (PERMANOVA)). The results showed that the differences in the bacterial community structure diversity within the blank group, the model group, and the Huangqin decoction administration group were significantly smaller than the differences between the groups, suggesting that the blank group, the model group, and the Huangqin decoction administration group had significant effects on the bacterial community structure diversity. There were significant between-group differences, see Table 2.

3.3.5. Gut Microbiota Difference Analysis. Using the method of random forest analysis, we screened the different gut microbiota among the experimental groups. We found that the gut microbiota with differences at the phylum level included deferribacteres, Proteobacteriae, tenericutes, Firmicutes, acidobacteria, cyanobacteria, Actino bacteriae, Bacteroidetes, fusobacteria, tm7-3, Chloroflexi, and WS6. The gut microbiota with differences at the class level include Mollicutes, epsilon Proteobacteria, deferribacteres, deltaproteobacteria, Actinobacteriae, tenericutes, Betaproteobacteria, Alphaproteobacteria, synchococycophycideae, bacilli, [choloracidobacteria], Flavobacteria Chloroflexi, TM7-1, and Fusobacteriia. The gut microbiota with differences at the order level include deferribacteriales, desulfovibrioiales, bacillales, actinomycetales, campylobacteriales, bifidobacteria, caulobacteriales, enterobacteria, erysipelo trichi, betaproteobacteria, Alphaproteobacteria, synchococycophycideae, bacilli, [choloracidobacteria], Flavobacteria Chloroflexi, TM7-1, and Fusobacteriia. The gut microbiota with differences at the family level include [paraprevotellaceae], corynebacteriaceae, Veillonella CEA, [odoribacterae], prevotellaceae, deferribacterae, staphylococcaceae, Rhodospirillaceae, anaeroplasmataceae, caulobacteraceae, streptococ caceae, dehalobactriacae, christensenellaceae, desulfovibrionaceae, ruminococcaceae, F16 Bifidobacteriaceae, Helicobacteraceae, S24-7, and Pianococccaceae; gut microbiota groups that differ at the genus level include [Prevotella], blautia, bilophila, Corynebacterium, Prevotella, Helicobacter, Lactococcus, rikenella, parabacteroides, anaeroplasma, Megaspheara, dehalobacterium, oscillospira, Clostridium, Streptococcus, Shigella, AF12, Desulfovibrio, and Candidatus_Arthromitus; the gut microbiota that produce differences at the species level Parabacteroides_distasonis, Mucispirillum_schaedleri, Al sistipes_indistinctus, Bacteroides_uniformis, Corynebacterium_ stationis, Lactobacillus_helveticus, Desulfovibrio_C21_c20, [Ruminococcus]_gnavus, Al listipes_finegoldii, Al listipes_onderdonkii, Sulfurcurvum_kujiense, Cellulomonas_uda, Butyricoccus_pullicaecorum, Lactobacillus_vagini, Silene_vulgaris, Staphylococcus_sciuri, Helicobacter_hepaticus, Cetobacterium_somerae, Al listipes_massiliensis, Clostridium_cocleatum; by observing the gut microbiota with different levels of phyla and genus, it is found that there are 6 species of gut microbiota with callback effect at phyla level, namely, TM7, tenericutes, Chloroflexi, cyanobacteria, acidobacteria, and WS6. There are 5 gut microbiota species with callback effect at the genus level, namely, [Prevotella], Helicobacter, Prevotella, Lactococcus, and anaeroplasma, as shown in Figure 5.

3.3.6. Prediction of Metabolic Pathways in Microbiota Sample Communities. In order to identify the signaling pathway of Huangqin decoction in the treatment of DE, this study used picurst2 to perform functional analysis on the treatment group and identified 170 signaling pathways through enrichment, as shown in Table 3 below.

3.4. Network Pharmacology Analysis. After entering the keyword, “Scutellaria baikalensis, Paeonia alba, jujube and licorice” in the TCMSP database, 34 effective components of Scutellaria baikalensis, 8 effective components of Paeonia alba, 20 effective components of jujube, and 90 effective components of licorice were screened according to the screening conditions of OB ≥ 30% and DL ≥ 0.18. After merging and deleting multiple items, 141 components were obtained, as shown in Table 4. Using PubChem database

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**Table 4: Continued.**

| MOL ID       | Ingredient                                                                 | OB (%)         | DL Source | Source          |
|--------------|------------------------------------------------------------------------------|----------------|-----------|-----------------|
| MOL008206    | Mosoolsflavone                                                             | 44.08795959    | 0.25331   |                 |
| MOL010415    | 11,13-Eicosaioenoic acid, methyl ester                                     | 39.27534422    | 0.2289    |                 |
| MOL012245    | 5,7,4'-Trihydroxy-6-methoxyflavanone                                       | 36.62688628    | 0.26833   |                 |
| MOL012246    | 5,7,4'-Trihydroxy-8-methoxyflavanone                                       | 74.23522001    | 0.26479   |                 |
| MOL012266    | Rivularin                                                                  | 37.94023355    | 0.3663    |                 |
| MOL002776    | Baicalin                                                                    | 40.12          | 0.75      |                 |
| MOL001918    | Paeoniforgenone                                                            | 87.59312084    | 0.36678   |                 |
| MOL001919    | (3S,5R,8R,9R,10S,14S)-3,17-dihydroxy-4,4,8,10,14-pentamethyl-2,3,5,6,7,9-hexahydro-1H-cyclopenta[a]phenanthrene-15,16-dione | 43.55620167    | 0.53276   | White peony root |
| MOL001924    | Paeoniflorin                                                               | 53.87037516    | 0.78709   |                 |
Table 5: Target information of DE in network pharmacology.

| No. | Gene names | Protein names | Uniprot ID |
|-----|------------|---------------|------------|
| 1   | TGFB1      | Transforming growth factor beta-1 proprotein | P01137 |
| 2   | SLC6A4     | Sodium-dependent serotonin transporter | P31645 |
| 3   | PTGS2      | Prostaglandin G/H synthase 2 | P35354 |
| 4   | PTGS1      | Prostaglandin G/H synthase 1 | P23219 |
| 5   | PRKCA      | Protein kinase C alpha type | P17252 |
| 6   | PRKACA     | cAMP-dependent protein kinase catalytic subunit alpha | P17612 |
| 7   | PON1       | Serum paroxonase/arylesterase 1 | P27169 |
| 8   | PIK3CG     | Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit gamma isoform | P48736 |
| 9   | OPRM1      | Mu-type opioid receptor | P35372 |
| 10  | JUN        | Transcription factor AP-1 | P05412 |
| 11  | HTR2A      | 5-Hydroxytryptamine receptor 2A | P28223 |
| 12  | HSP90AA1   | Heat shock protein HSP 90-alpha | P07900 |
| 13  | CASP9      | Caspase-9 | P55211 |
| 14  | CASP8      | Caspase-8 | Q14790 |
| 15  | CASP3      | Caspase-3 | P42574 |
| 16  | BCL2       | Apoptosis regulator Bcl-2 | P10415 |
| 17  | BAX        | Apoptosis regulator BAX | Q07812 |
| 18  | ADRB2      | Beta-2 adrenergic receptor | P07550 |
| 19  | NR3C2      | Mineralocorticoid receptor | P08235 |
| 20  | XDH        | Xanthine dehydrogenase/oxidase | P47989 |
| 21  | VCAM1      | Vascular cell adhesion protein 1 | P19320 |
| 22  | TNF        | Tumor necrosis factor | P01375 |
| 23  | STAT1      | Signal transducer and activator of transcription 1-alpha/beta | P42224 |
| 24  | SLPI       | Antileukoproteinase | P03973 |
| 25  | SLC2A4     | Solute carrier family 2, facilitated glucose transporter member 4 | P14672 |
| 26  | SELE       | E-selectin | P16581 |
| 27  | RELA       | Transcription factor p65 | Q04206 |
| 28  | PRSS1      | Trypsin-1 | P07477 |
| 29  | PPARG      | Peroxisome proliferator-activated receptor gamma | Q08209 |
| 30  | NOS3       | Nitric oxide synthase, endothelial | P37231 |
| 31  | NOS2       | Nitric oxide synthase, inducible | Q14994 |
| 32  | MMP1       | Interstitial collagenase | O75469 |
| 33  | MAPK8      | Mitogen-activated protein kinase 8 | P29474 |
| 34  | INSR       | Insulin receptor | P35228 |
| 35  | IKBKB      | Inhibitor of nuclear factor kappa-B kinase subunit beta | P03956 |
| 36  | ICAM1      | Intercellular adhesion molecule 1 | P45983 |
| 37  | HMOX1      | Heme oxygenase 1 | P06213 |
| 38  | GSTM1      | Glutathione S-transferase Mu 1 | O14920 |
| 39  | F7         | Coagulation factor VII | P05362 |
| 40  | F2         | Prothrombin | P09601 |
| 41  | DPP4       | Dipeptidyl peptidase 4 | P09488 |
| 42  | CYP3A4     | Cytochrome P450 3A4 | P08709 |
| 43  | CYP1A1     | Cytochrome P450 1A1 | P00734 |
| 44  | CDK1       | Cyclin-dependent kinase 1 | P27487 |
| 45  | AR         | Androgen receptor | P08684 |
| 46  | ALOX5      | Polyunsaturated fatty acid 5-lipoxygenase | P04798 |
| 47  | AKT1       | RAC-alpha serine/threonine-protein kinase | P06493 |
| 48  | AHR        | Aryl hydrocarbon receptor | P10275 |
Table 5: Continued.

| No. | Gene names | Protein names | Uniprot ID |
|-----|------------|---------------|------------|
| 49  | ACHEx      | Acetylcholinesterase | P09917     |
| 50  | ESR1       | Estrogen receptor  | P31749     |
| 51  | IL6        | Interleukin-6     | P35869     |
| 52  | CD14       | Monocyte differentiation antigen CD14 | P22303 |
| 53  | FASN       | Fatty acid synthase | P19793     |
| 54  | TP53       | Cellular tumor antigen p53 | P03372 |
| 55  | THBD       | Thrombomodulin     | P18428     |
| 56  | SPP1       | Osteopontin        | P05231     |
| 57  | SOD1       | Superoxide dismutase [Cu-Zn] | P08571 |
| 58  | SERPINE1   | Plasminogen activator inhibitor 1 | P49327 |
| 59  | RUNX2      | Runt-related transcription factor 2 | P04637 |
| 60  | RB1        | Retinoblastoma-associated protein | P07204 |
| 61  | RAF1       | RAF protooncogene serine/threonine-protein kinase | P10451 |
| 62  | PTEN       | Phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN | P00441 |
| 63  | PRKCB      | Protein kinase C beta type | P05121 |
| 64  | PPARD      | Peroxisome proliferator-activated receptor delta | Q13950 |
| 65  | PPARA      | Peroxisome proliferator-activated receptor alpha | P06400 |
| 66  | PLAU       | Urokinase-type plasminogen activator | P04049 |
| 67  | PLAT       | Tissue-type plasminogen activator | P60484 |
| 68  | PARP1      | Poly [ADP-ribose] polymerase 1 | P05771 |
| 69  | ODC1       | Ornithine decarboxylase | Q03181 |
| 70  | NQO1       | NAD | Q07869 |
| 71  | NFKBIA     | NF-kappa-B inhibitor alpha | P00749 |
| 72  | NFE2L2     | Nuclear factor erythroid 2-related factor 2 | P00750 |
| 73  | NCF1       | Neutrophil cytosol factor 1 | P09874 |
| 74  | MYC        | Myc protooncogene protein | P11926 |
| 75  | MPO        | Myeloperoxidase | P15559 |
| 76  | MMP9       | Matrix metalloproteinase-9 | P25963 |
| 77  | MMP3       | Stromelysin-1 | Q16236 |
| 78  | MMP2       | 72 kDa type IV collagenase | P01106 |
| 79  | MIPAM      | Maltase-glucoamylase, intestinal [includes: maltase | P05164 |
| 80  | MAPK1      | Mitogen-activated protein kinase 1 | P14780 |
| 81  | IL2        | Interleukin-2 | P08254 |
| 82  | IL1B       | Interleukin-1 beta | P08253 |
| 83  | IL1A       | Interleukin-1 alpha | O43451 |
| 84  | IL10       | Interleukin-10 | P28482 |
| 85  | IGFBP3     | Insulin-like growth factor-binding protein 3 | P60568 |
| 86  | IGF2       | Insulin-like growth factor II | P01584 |
| 87  | IFNG       | Interferon gamma | P01583 |
| 88  | HSPB1      | Heat shock protein beta-1 | P22301 |
| 89  | HSPA5      | Endoplasmic reticulum chaperone BiP | P17936 |
| 90  | HK2        | Hexokinase-2 | P01344 |
| 91  | HIF1A      | Hypoxia-inducible factor 1-alpha | P01579 |
| 92  | GJA1       | Gap junction alpha-1 protein | P04792 |
| 93  | FOS        | Protooncogene c-Fos | P11021 |
| 94  | F3         | Tissue factor | P52789 |
| 95  | ERBB3      | Receptor tyrosine-protein kinase erbB-3 | Q16665 |
| 96  | ERBB2      | Receptor tyrosine-protein kinase erbB-2 | P17302 |
| No. | Gene names | Protein names | Uniprot ID |
|-----|------------|---------------|------------|
| 97  | EGFR       | Epidermal growth factor receptor | P01100     |
| 98  | CXCL8      | Interleukin-8 | P13726     |
| 99  | CXCL10     | C-X-C motif chemokine 10 | P00742     |
| 100 | CTSD       | Cathepsin D   | P21860     |
| 101 | CRP        | C-reactive protein [cleaved into: C-reactive protein] | P4626      |
| 102 | CLDN4      | Claudin-4     | P00533     |
| 103 | CHEK2      | Serine/threonine-protein kinase Chk2 | Q01094    |
| 104 | CDKN1A     | Cyclin-dependent kinase inhibitor 1 | P10145    |
| 105 | CD40LG     | CD40 ligand   | P19875     |
| 106 | CCND1      | G1/S-specific cyclin-D1 | P02778    |
| 107 | CCL2       | C-C motif chemokine 2 | P07339    |
| 108 | CAV1       | Caveolin-1    | P02741     |
| 109 | BIRC5      | Baculoviral IAP repeat-containing protein 5 | P02461    |
| 110 | AKR1B1     | Aldo-keto reductase family 1 member B1 | Q96017    |
| 111 | ACACA      | Acetyl-CoA carboxylase 1 | P38936    |
| 112 | ADRB1      | Beta-1 adrenergic receptor | P29965    |
| 113 | ADRA2A     | Alpha-2A adrenergic receptor | P24385    |
| 114 | HTR2C      | 5-Hydroxytryptamine receptor 2C | P13500    |
| 115 | DRD4       | D             | Q03135     |
| 116 | ADRA2B     | Alpha-2B adrenergic receptor | O15392    |
| 117 | PDE4D      | cAMP-specific 3′,5′-cyclic phosphodiesterase 4D | Q07817    |
| 118 | KDR        | Vascular endothelial growth factor receptor 2 | P15121    |
| 119 | HTR3A      | 5-Hydroxytryptamine receptor 3A | Q13085    |
| 120 | CTNNB1     | Catenin beta-1 | P21397    |
| 121 | DRD2       | D             | P08588     |
| 122 | ESR2       | Estrogen receptor beta | P35968    |
| 123 | CDK2       | Cyclin-dependent kinase 2 | P35222    |
| 124 | PTPN1      | Tyrosine-protein phosphatase nonreceptor type 1 | P55210    |
| 125 | OLR1       | Oxidized low-density lipoprotein receptor 1 | P14416    |
| 126 | MAPK14     | Mitogen-activated protein kinase 14 | P20813    |
| 127 | GSK3B      | Glycogen synthase kinase-3 beta | Q92731    |
| 128 | SIRT1      | NAD-dependent protein deacetylase sirtuin-1 | P24941    |
| 129 | MT-ND6     | NADH-ubiquinone oxireductase chain 6 | P18031    |
| 130 | IL4        | Interleukin-4 | P78380     |
| 131 | STAT3      | Signal transducer and activator of transcription 3 | Q16539    |
| 132 | CDK4       | Cyclin-dependent kinase 4 | P49841    |
| 133 | JAK2       | Tyrosine-protein kinase JAK2 | Q96EB6    |
| 134 | SLC2A1     | Solute carrier family 2, facilitated glucose transporter member 1 | P03923    |
| 135 | MAPK10     | Mitogen-activated protein kinase 10 | P05112    |
| 136 | SREBF1     | Sterol regulatory element-binding protein 1 | P40763    |
| 137 | SOAT1      | Sterol O-acyltransferase 1 | P11802    |
| 138 | MTPP       | Microsomal triglyceride transfer protein large subunit | O60674    |
| 139 | MAPK3      | Mitogen-activated protein kinase 3 | P11166    |
| 140 | LDLR       | Low-density lipoprotein receptor | P53779    |
| 141 | HMGCR      | 3-Hydroxy-3-methylglutaryl-coenzyme A reductase | P36956    |
| 142 | GSR        | Glutathione reductase, mitochondrial | P55157    |
| 143 | CYP19A1    | Aromatase     | P27361     |
| 144 | BAD        | Bcl2-associated agonist of cell death | P01130    |
According to KEGG enrichment analysis, the significant pathways are bladder cancer, colorectal cancer, pancreatic cancer, leishmaniasis, hepatitis B, etc.

To identify the main genes of Huangqin decoction’s anti-DE (Table 5), Cytoscape 3.8.2 was used for visual analysis, and a protein-protein interaction network was constructed (Figure 6(c)). At the same time, the cytohubba plug-in was used to screen out the core targets. Combined with the score of the calculation method, the top 10 genes were considered as core genes (IL-6, TNF, TP53, IL1B, CASP3, JUN, PPARC, MAPK3, EGFR, and PTGS2).

Table 6. GO annotation and KEGG pathway enrichment of the obtained potential target genes of Huangqin decoction for the treatment of DE were performed by R language (Figures 6(d) and 6(e)). GO enrichment analysis showed that there was mainly positive regulation of nitric oxide biosynthetic process, response to ethanol, response to hypoxia, etc. According to KEGG enrichment analysis, the significantly affected pathways are bladder cancer, colorectal cancer, pancreatic cancer, leishmaniasis, hepatitis B, etc.

3.5. Integrating 16S rRNA Gene Sequencing and Network Pharmacology Analysis. In order to identify the signaling pathway of Huangqin decoction in the treatment of DE, this study used picurst2 to analyze the function of the treatment group and identified 170 signaling pathways through enrichment. Similar signaling pathways are followed by apoptosis (apoptosis), calcium signaling pathway (calcium signaling pathway), cell cycle-Caulobacter (cell cycle-Caulobacter), insulin signaling pathway (insulin signaling pathway), neurotrophin signaling pathway (neurotrophin signaling pathway), NOD-like receptor signaling pathway, and RIG-I-like receptor signaling pathway. Based on the core genes obtained from these seven signaling pathways and network pharmacology, an integrated network map of Huangqin decoction for the treatment of DE was drawn. As shown in Figure 7, the NOD-like receptor signaling pathway has the most significant node, and it has the strongest correlation with TNF and quercetin. Therefore, it is speculated that the mechanism of Huangqin decoction in the treatment of DE may be that the core component of Huangqin decoction, quercetin inhibits the expression of the TNF gene, thereby inhibiting the expression of NOD-like receptor signaling pathway and thereby achieving the therapeutic effect of the disease.

4. Discussion

This study combined network pharmacology and 16S rRNA sequencing. This study screened 156 active ingredients of Huangqin decoction in treating DE. Among them, quercetin as the core active ingredient, also known as quercetin, is a flavonoid compound with various biological activities. Quercetin and its derivatives are widely distributed in the plant kingdom, mostly in flowers, leaves, and fruits. Exist in the form of glycosides. It has expectorant, antitussive, antiasthmatic, anti-inflammatory, anti-inflammatory, anti-allergic, antiarrhythmic, antiplatelet aggregation, antioxidant, antitumor, antioxidant, antidiabetic complications, and other pharmacological effects [18]. Ling and others showed that the mechanism of quercetin treatment in type 2 diabetic rats was that the substance activated the FGF21/MAPK signaling pathway in the pancreatic tissue increased the expression level of FGF21 and MAPK.

In contrast, the high level of FGF21 could significantly reduce the bodyweight of type 2 diabetic rats and accelerate the reabsorption of blood glucose, thereby lowering the level of blood sugar. β function of cells was maintained and played a role in improving insulin resistance. MAPK is the key kinase downstream of FGF21. This enzyme accelerates the absorption and utilization of sugars by increasing the expression of GLUT4, and the increase of insulin receptor sensitivity and insulin resistance is achieved through MAPK phosphorylation to achieve the effect of treating type 2 diabetes [19]. Mao Xiaoming et al. found that quercetin can inhibit the activity of aldose reductase in the diabetic kidney by measuring the urinary protein in the kidney tissue of experimental diabetic rats, and early application can prevent...
Figure 6: Continued.
Positive regulation of nitric oxide biosynthetic process
Response to ethanol
Response to hypoxia
Aging
Response to drug
Positive regulation of gene expression
Negative regulation of apoptotic process
Positive regulation of transcription from RNA polymerase II promoter

Caveola
Membrane raft
Extracellular space
Extracellular region
Cytosol
Plasma membrane
Enzyme binding
Transcription factor binding
Protein kinase binding
Identical Protein binding
Protein homodimerization activity
Protein binding

Fold enrichment

Count
25
50
75
100
125

Figure 6: Continued.
or delay the occurrence of diabetes [20]; in the research on the protective mechanism of quercetin on the kidneys of diabetic rats, it was found that quercetin can improve oxidative stress and have anti-inflammatory effects, thereby exerting a protective effect on early diabetes [21].

Tumor necrosis factor (TNF) has typical cytokine properties and is a major inflammatory factor and pleiotropic cellular regulatory protein. The excessive local release can trigger an inflammatory response and the body’s immune response process. This factor is closely related to insulin and promotes insulin resistance by interfering with the insulin signal transduction pathway, resulting in the clinical manifestations of insulin resistance [22]. The KEGG signaling pathway enrichment results showed that the most

![Diagram of enriched pathways](image)

### Table 6: CytoHubba key genes screened.

| Gene symbol | MCC  | MNC  | Degree | EPC  | Rank methods in CytoHubba | BottleNeck | EcCentricity | Closeness | Radiality | Betweenness | Stress |
|-------------|------|------|--------|------|---------------------------|------------|--------------|-----------|----------|-------------|--------|
| IL-6        | 9.22E+13 | 123 | 246    | 25.989 | 24                        | 0.5        | 0.5          | 139       | 3.82581  | 1344.73372  | 83272  |
| TNF         | 9.22E+13 | 117 | 234    | 25.101 | 1                         | 0.5        | 0.5          | 136       | 3.7871   | 874.01279   | 78512  |
| TP53        | 9.22E+13 | 116 | 232    | 23.732 | 2                         | 0.5        | 0.5          | 135.5     | 3.78065  | 771.82047   | 70320  |
| IL1B        | 9.22E+13 | 110 | 220    | 25.059 | 1                         | 0.33333    | 132.33333    | 3.73548   | 506.5106 | 50800       |        |
| CASP3       | 9.22E+13 | 106 | 212    | 23.827 | 5                         | 0.33333    | 130.33333    | 3.70968   | 520.91581| 53936       |        |
| JUN         | 9.22E+13 | 104 | 208    | 23.701 | 1                         | 0.33333    | 129.33333    | 3.69677   | 383.48979| 42960       |        |
| PPARG       | 9.22E+13 | 101 | 202    | 23.55  | 1                         | 0.33333    | 127.83333    | 3.67742   | 309.07813| 36088       |        |
| MAPK3       | 9.22E+13 | 99  | 198    | 24.044 | 37                        | 0.5        | 127          | 3.67097   | 555.13067| 49336       |        |
| EGFR        | 9.22E+13 | 98  | 196    | 23.689 | 1                         | 0.5        | 126.5        | 3.66452   | 354.85078| 40368       |        |
| PTGS2       | 9.22E+13 | 95  | 190    | 23.301 | 1                         | 0.5        | 125          | 3.64516   | 700.314  | 59256       |       |
prominent signaling pathway was NOD-like receptor signaling pathway. Relevant studies have shown that the innate immune system can recognize a variety of pathogenic microorganisms and is the body’s first line of defense against pathogenic microorganisms. It recognizes invading pathogens by sensing pathogen-associated molecular patterns through specialized pattern recognition receptors (PRRs). They can be recognized by PRR-containing immune cells to initiate an immune response [23]. Among them, the NOD-like receptor family (NLR) is cytoplasmic, as one of the pattern recognition receptors, greatly influences the disease. NOD1 and NOD2 are members of the NODs subtypes of the NLRs family. NOD1 and NOD2 are cytoplasmic receptors for innate immunity that sense peptidoglycan from Gram-negative bacteria. Their functions have been extensively studied [24–26], revealing that they play a key role in host defense against pathogens such as Listeria monocytogenes, Helicobacter pylori, and Staphylococcus. In humans, dysregulation of NOD signaling pathways caused by mutations in NOD receptors, especially NOD2 receptors, is associated with inflammatory bowel disease. At the same time, related studies have found that NOD2 can recognize bacterial-derived cell muramyl dipeptide, which can induce the release of antimicrobial peptides and inflammatory signals required to maintain the homeostasis of intestinal flora, thereby protecting the host from bacterial invasion and thereby playing a role in preventing and treating diabetes. The expression of NOD2 is induced by bacterial components (lipopolysaccharide LPS), short-chain fatty acids (butyric acid), hormone vitamin D (1,25-dihydroxyvitamin D3), and proinflammatory cytokines (TNF-α), among others [27]. This is also consistent with the results of this experiment.

Some human diseases, including inflammatory bowel disease (IBD), diabetes, obesity, metabolic syndrome, fatty liver, and some neurological diseases, have been confirmed to be related to intestinal flora imbalance. The continuous exposure of intestinal tissue to microorganisms puts the intestinal mucosa in a state of physiological inflammation, where proinflammatory and anti-inflammatory responses are in balance to maintain body homeostasis [28]. If this relationship is unbalanced, it will lead to dysbiosis, where pathogenic bacteria dominate the commensal bacteria, causing damage to the intestinal epithelial barrier, bacterial invasion, and inflammation [29, 30]. To date, multiple studies have highlighted the important role of Nod2 in maintaining the balance between the microbial community and the host immune response [31, 32]. At the same time, the 16S rRNA results were consistent with it. In this study, we found 6 species of bacteria with callback effect at the phylum level, namely, TM7, Tenericutes, Chloroflexi, Cyanobacteria, Acidobacteria, and WS6. Among them, TM7 and Tenericutes are in the callback function. The most important value ranks among the phyla, and the research species related to diabetes are considered to be related to the inflammatory response. Tenericutes is the third dominant bacterial phylum in this study, which has been reported to be involved in the occurrence and development of diabetes. This study is closely related to the inflammatory response caused by high glucose, and the inhibition of Softwallia helps control the inflammatory response related to diabetes [33]. The proportions of TM7 were 2.48%, 5.55%, and 0.88%, respectively, and there was an obvious correction. TM7 was the sixth bacterial phylum in this study, which was confirmed to be positively correlated with the occurrence of inflammation in diabetes [34]; the genus level had a callback. There are 5 species of bacteria that act, namely, [Prevotella], Helicobacter, Prevotella, Lactococcus, and Anaeroplasma. Prevotella is the genus with the highest significant value in this study, and its level reduction is considered to be related to the inhibition of diabetes. These changes are related to the inflammatory responses [35, 36]. These changes indicate that Huangqin decoction can regulate the intestinal flora of diabetic mice. By regulating the abundance of bacteria, it protects the intestinal mucosa, improves the intestinal barrier function, and inhibits the inflammatory response generated in the high glucose state.

Figure 7: Comprehensive network diagram of Huangqin decoction in the treatment of DE.
5. Conclusion

Through network pharmacology and 16S rRNA sequencing analysis, it was found that the mechanism of Huangqin decoction in the treatment of DE may be the prevention and treatment of the disease by inhibiting the expression of inflammatory factors in intestinal epithelial cells, thereby regulating the intestinal flora, but the exact molecular mechanism remains to need further verified.

Abbreviations

DE: Diabetic enteritis
GO: Gene Ontology
KEGG: Kyoto Encyclopedia of Genes and Genomes
TCMSP: Traditional Chinese medicine systems pharmacology.

Data Availability

The data used to support this study are available from the corresponding author upon request.

Ethical Approval

All animal experiments were conducted following the relevant regulations of Heilongjiang University of Traditional Chinese Medicine’s experimental animal ethics committee.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors’ Contributions

Xiaomin XU conceived and designed the experiments; Cheng Fang conducted the experimental work and analysis; Shumin Liu provided major revisions and comments to the manuscript. All authors reviewed and approved the final manuscript. Xiaomin Xu and Cheng Fang contributed equally to this work.

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