Research Article

Network Pharmacology-Based Analysis of Gegenqinlian Decoction Regulating Intestinal Microbial Activity for the Treatment of Diarrhea

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Gegenqinlian decoction (GD) has been extensively used for the treatment of diarrhea with intestinal dampness-heat syndrome (IDHS) with a satisfying therapeutic effect. The purpose of this study is to clarify the active ingredients and mechanism of GD in the treatment of diarrhea with IDHS. The TCMSP database was used to screen out the active ingredients of the four Chinese herbal medicines in GD, and the targets of the active ingredients were predicted. We selected the targets related to diarrhea through the DisGeNET database, then used the NCBI database to screen out related targets of lactase and sucrase, and constructed the visual network to search for the active ingredients of GD in the treatment of diarrhea and related mechanisms of the targets. Combined with network pharmacology, we screened out 146 active ingredients in GD corresponding to 252 ingredient targets, combined with 328 disease targets in diarrhea, and obtained 12 lactase targets and 11 sucrase targets. The key active ingredients involved quercetin, formononetin, β-sitosterol kaempferol, and wogonin. Furthermore, molecular docking showed that these five potential active ingredients had good affinities with the core targets PTGS2. The active ingredients in GD (such as quercetin, formononetin, and β-sitosterol) may increase the microbial activity of the intestinal mucosa of mice and reduce the microbial activity of the intestinal contents through multiple targets, thereby achieving the effect of treating diarrhea.

1. Introduction

Syndrome research has always been the core content of traditional Chinese medicine (TCM) academic research. Research on the nature of syndromes and animal models of syndromes plays a beneficial role in revealing the scientific connotation of syndromes and the objectification of syndromes. Diarrhea with intestinal damp heat syndrome (IDHS) refers to the accumulation of dampness-heat in the intestinal tract, which is mainly manifested by abdominal pain, urgency of diarrhea, and yellowish brown and stinky feces [1]. With the changes of people’s lifestyle and diet structure, IDHS diarrhea has become a multiple disease. Diabetes, chronic liver disease, kidney disease, ulcerative colitis, and other diseases are often accompanied by IDHS diarrhea. Therefore, strengthening the study of diarrhea with IDHS can expand the prevention and treatment of these major diseases.

Intestinal microorganisms are closely related to the physiology, pathology, and treatment of diseases of the body [2–4]. These can secrete a variety of enzymes, participate in the decomposition and transformation of food in the intestine, and provide energy for the growth and development of the body [5]. The occurrence of diarrhea with IDHS is often accompanied by intestinal microbial imbalance, which is bound to affect intestinal enzyme activity [6]. It was found that the activity of lactase in the intestinal tract of diarrhea irritable bowel syndrome rats was significantly lower than that of the control group (p < 0.05), and the activity of sucrase in the intestinal contents and...
mucosa of mice with dysbacteriosis and diarrhea was significantly decreased compared with the control group (p < 0.01) [7, 8]. Different kinds of enzymes reflect the active degree of microbial participation in biochemical reactions, while microbial activity often represents the overall activity of hydrolyses and can be used as an important indicator of microbial decomposition ability [9, 10]. As a colorless nonpolar organic compound, fluorescein diacetic acid (FDA) can be hydrolyzed by nonspecific enzymes (esterase, protease, lipase, etc.) in bacteria and fungi, and its hydrolytic activity is directly proportional to the number of microbial populations [11]. Therefore, the total activity of microorganisms in the animal intestinal tract can be reflected by measuring the degree of FDA hydrolysis of intestinal samples.

Gegenqinlian decoction (GD), as a classic prescription for diarrhea with IDHS, is composed of Pueraria Lobatae Radix (Pueraria lobata (Willd.) Ohwi), Scutellariae Radix (Scutellaria baicalensis Georgi), Coptidis Rhizoma (Coptis chinensis Franch), and Glycyrrhizae Radix Et Rhizoma (Glycyrrhiza uralensis Fisch). It is better for clearing away heat and dampness, distributing benefits, and stopping diarrhea. GD is widely used in the treatment of diabetes, hypertension, hyperlipidemia, obesity, and other diseases, with significant effects [12–14]. Modern pharmacological studies have indicated that GD has antipyretic, anti-inflammatory, antibacterial, and immunological improvement and intestinal microbial regulation functions [15–17]. Oral drugs enter the small intestine through the upper digestive tract and are digested and absorbed, which play an effective role by inhibiting or inducing the enzyme activity in the intestine [18]. Therefore, exploring the effect of the active ingredients in GD on the regulation of intestinal enzyme activity in diarrhea with IDHS has become the focus of this study.

As an emerging science based on a multilayered network of disease-gene-drug, network pharmacology has been widely used to screen active ingredients, explain the overall action mechanisms, and study the pathogenesis of diseases. While the multiple ingredients of TCM have curative effects on multiple targets of diseases, network pharmacology can visualize, systematize, and inform the process principles of TCM in treating diseases [19]. A growing body of evidence suggested that the holistic concept of TCM had many similarities with the core ideas of the emerging network pharmacology and was more often applied in the treatment of complex diseases, which provided a new research strategy for the development of network pharmacology of TCM [20]. Based on these, synthesized with the previous experimental results of our research group, the effect of GD on the intestinal microbial activity of diarrhea with IDHS mice was explored to clarify the microecological mechanism of its therapeutic effect [21]. Through the overall process of screening active ingredients, network construction, and analysis, GD-active ingredients and candidate targets were predicted, and the pharmacodynamic substances and targets of GD in the treatment of diarrhea were sought, so as to provide basis for the diagnosis and treatment of syndrome differentiation in clinical diarrhea and the study on the therapeutic mechanism of TCM prescriptions.

2. Materials and Methods

2.1. Collection of Active Ingredients and Targets of GD. We input Pueraria Lobatae Radix (PLR), Scutellariae Radix (SR), Coptidis Rhizoma (CR), and Glycyrrhizae Radix Et Rhizoma (GRER) into the Traditional Chinese Medicine Systems Pharmacology (TCMSP, http://tcmspw.com/index.php) database [22] to retrieve the Chinese herbal medicine ingredients, setting oral bioavailability (OB) ≥ 30% and drug-likeness (DL) ≥ 0.18 for further screening that will meet the conditions of TCM composition as the active ingredients. Then, we searched the targets of the active ingredients through the TCMSP database and entered the obtained protein name into the Universal Protein (UniProt, https://www.uniprot.org/) database [23] to find the corresponding gene name of each target to facilitate subsequent analysis.

2.2. Prediction of Potential Targets for Diarrhea. Potential genes associated with diarrhea were collected from DisGeNET (https://www.disgenet.org/) [24]. For filtering the targets, “diarrhea” was defined as the key word and results were restricted to “Homo sapiens.” After integration of search-derived target data and elimination of the repeated genes, the therapeutic target database was obtained.

2.3. Construction of the Diarrhea-Potential Target-Enzyme Network. The lactase and sucrase were input in the National Center for Biotechnology Information (NCBI https://www.ncbi.nlm.nih.gov/) database [25] to retrieve related targets, and the source of species was set for “Homo sapiens” for further screening. Then, we imported the potential targets of the disease and lactase and sucrase into Cytoscape 3.7.2 software to construct a network diagram of diarrhea-potential targets-enzymes.

2.4. Construction of the GD-Potential Active Ingredient-Potential Target-Enzyme Network. The lactase and sucrase were input in the NCBI database (https://www.ncbi.nlm.nih.gov/) [25] to retrieve related targets, and the source of species was set for “Homo sapiens” for further screening. Then, we imported the GD-potential targets and their corresponding active ingredients and lactase and sucrase into Cytoscape 3.7.2 software to construct a network diagram of GD-potential active ingredients-potential targets-enzymes.

2.5. Construction of the GD-Potential Active Ingredient-Enzyme-Diarrhea Network. We import the GD-potential targets and their corresponding active ingredients, the disease targets, and the potential targets of lactase and sucrase into the Cytoscape 3.7.2 software [26], constructing the GD-potential active ingredient-enzyme-diarrhea network diagram.
2.6. Molecular Docking. Molecular docking verification of key active ingredients and key targets in GD-potential active ingredients-enzymes-diarrhea was carried out. The 3D structure of the key potential target was downloaded from the Protein Data Bank [27] (PDB, http://www.rcsb.org) database. We used AutoDock Tools software to remove water, separate ligands and hydrogenate, and calculate charge for the target proteins and used it as the receptor macromolecules. Then, we downloaded the structure diagram of the potential active ingredients of Chinese medicine in the ZINC 15 [28] (http://zinc.docking.org/) database, used the AutoDock Tool (version 1.5.6, http://autodock.scripps.edu/) to add charges, assign atom types, and confirm rotatable flexible bonds, and used it as the small ligand molecules. Finally, the docking results of active compounds and protein targets were visualized with PyMOL software (version 2.2, https://pymol.org/2/).

3. Results

3.1. GD-Active Ingredient-Potential Target-Enzyme Network Analysis. GD-active ingredient and target information was retrieved from the TCMSP database. There were 146 active ingredients of GD that met OB ≥ 30% and DL ≥ 0.18, including 4 PLR, 36 SR, 14 CR, and 92 GRER. Entering these into the TCMSP database, a total of 2660 targets were found in the search, and 269 targets were obtained after deleting duplicate values. These targets were input into the UniProt database for conversion, and after the final deduplication, only 252 targets successfully found the corresponding gene names. The relevant information of the GD-active ingredients is shown in Table 1. Then, 146 potential active ingredients corresponding to 4 Chinese medicines in GD, 12 lactase targets (e.g., LCT, GLB1, LCTL, MCM6, and HNF1A), and 11 sucrase targets (e.g., LCT, GLB1, LCTL, MCM6, and HNF1A) were input into Cytoscape 3.7.2 software, and the GD-active ingredient-potential target-enzyme network was constructed (Figure 1). The network consisted of 407 nodes and 2717 edges, among which the purple triangles represented 4 Chinese herbal medicines, the blue circles represented the active ingredients, the green hexagons represented lactase and sucrase, and the yellow diamonds represented the targets. Through the network analysis tool in Cytoscape 3.7.2 software, we screened the active ingredients that mainly played a role according to the “degree” value. The greater the degree value, the more the connection points of the ingredients and the greater the effect. The top active ingredients were quercetin, formononetin, beta-sitosterol, kaempferol, and wogonin. Among them, quercetin is shared by 2 Chinese herbal medicines, with 284 targets including PTGS2, HSP90, CALM, AR, and ESR1, which interacted with 122, 95, 94, 93, and 92 targets (Table 2). Based on these, we found the phenomenon that some ingredients in GD could act on multiple targets, and different ingredients worked together on the same target, which might reflect the mechanism of interaction between multiple compounds and multiple targets in TCM. Through analysis, the ingredients in the network that were closely related to the targets are quercetin, formononetin, beta-sitosterol, kaempferol, and wogonin, indicating that the two active ingredients in GD may be crucial in regulating enzyme activity in the treatment of diarrhea.

3.2. Diarrhea-Potential Target-Enzyme Network Analysis. 328 diarrhea-related targets were collected through the DisGeNET database. Then, we constructed the diarrhea-potential target-enzyme network (Figure 2). In this network, there were 347 nodes and 351 connections in the network. Pink hexagons represented diseases, green octagons represented lactase and sucrase, and yellow diamonds represented potential targets. The connection between nodes indicated the corresponding relationship between the two. The more the target points were connected, the more critical role the targets played in the network. The most connected target in the network was HNF1A, indicating that this target might play an important role in diarrhea affecting lactase and sucrase.

3.3. GD-Active Ingredient-Enzyme-Diarrhea Network Analysis. We input the 146 active ingredients of GD and 258 potential targets of diarrhea, as well as the potential targets of lactase and sucrase, into Cytoscape 3.7.2 software to construct the GD-active ingredient-enzyme-diarrhea network (Figure 3). There was a total of 408 nodes and 2748 connections in the network. Purple triangles represented 4 Chinese herbal medicines in GD, blue circles represented active ingredients in GD, pink hexagons represented diseases, green octagons represented lactase and sucrase, and yellow diamonds represented potential targets. From the perspective of ingredients, there were 18 ingredients with a target greater than thirty, of which 6 ingredients were greater than forty. By analyzing the degree centrality (DC), closeness centrality (CC), and betweenness centrality (BC) of the GD-active ingredient-enzyme-diarrhea network, the top five ingredients were quercetin, formononetin, beta-sitosterol, kaempferol, and wogonin, which could be interacted with 284, 76, 74, 58, and 45 target proteins work. As a view of the targets, the top five targets were PTGS2, HSP90, CALM, AR, and ESR1, which interacted with 122, 95, 94, 93, and 92 ingredients (Table 2). Based on these, we found the phenomenon that some ingredients in GD could act on multiple targets, and different ingredients worked together on the same target, which might reflect the mechanism of interaction between multiple compounds and multiple targets in TCM. Through analysis, the ingredients in the network that were closely related to the targets are quercetin, formononetin, beta-sitosterol, kaempferol, and wogonin, indicating that the two active ingredients in GD may be crucial in regulating enzyme activity in the treatment of diarrhea.

3.4. Molecular Docking Simulation. One potential target with five corresponding ingredients was simulated by molecular docking, and the docking results were analyzed. As far as we know, if the value of binding energy is less than 0 kJ/mol, this indicates that the ligand can spontaneously bind to the receptor. The molecular docking results showed that the molecular docking binding energy between the key chemical ingredients and the core target was less than 0 kJ/mol. Among them, formononetin and PTGS2 (~6.8 kcal·mol⁻¹), beta-sitosterol and PTGS2 (~5.61 kcal·mol⁻¹), and quercetin and PTGS2 (~4.86 kcal·mol⁻¹) have better binding energy, from which it can be seen that GD had good affinity and binding activity for core ingredient and key targets (Figure 4).
| Chinese medicine          | Mol ID   | Molecule Name                  | OB (%) | DL  |
|--------------------------|---------|--------------------------------|--------|-----|
| Puerariae Lobatae Radix  | MOL000392 | Formononetin                 | 69.67  | 0.21|
| Puerariae Lobatae Radix  | MOL000358 | beta-Sitosterol              | 36.91  | 0.75|
| Puerariae Lobatae Radix  | MOL002959 | 3'-Methoxydaidzein          | 48.57  | 0.24|
| Puerariae Lobatae Radix  | MOL003629 | Daidzein-4,7-diglucoside    | 47.27  | 0.67|
| Scutellariae Radix       | MOL002934 | Neobaicaelin                 | 104.34 | 0.44|
| Scutellariae Radix       | MOL002932 | Panicolin                    | 76.26  | 0.29|
| Scutellariae Radix       | MOL012246 | 5,7,4'-Trihydroxy-8-methoxyflavanone | 74.24 | 0.26|
| Scutellariae Radix       | MOL002927 | Skullcapflavone II          | 69.51  | 0.44|
| Scutellariae Radix       | MOL002911 | 2,6,2',4'-Tetrahydroxy-6'-methoxychalcone | 69.04 | 0.22|
| Scutellariae Radix       | MOL002937 | Dihydrooroxylin             | 66.06  | 0.23|
| Scutellariae Radix       | MOL000228 | (2R)-7-hydroxy-5-methoxy-2-phenylchroman-4-one | 55.23 | 0.2 |
| Scutellariae Radix       | MOL002915 | Salvigenin                   | 49.07  | 0.33|
| Scutellariae Radix       | MOL000073 | ent-Epicatechin               | 48.96  | 0.24|
| Scutellariae Radix       | MOL002917 | 5,2',6'-Trihydroxy-7,8-dimethoxyflavone | 45.05 | 0.33|
| Scutellariae Radix       | MOL008206 | Moslosolflavone             | 44.09  | 0.25|
| Scutellariae Radix       | MOL000449 | Stigmasterol                 | 43.83  | 0.76|
| Scutellariae Radix       | MOL001490 | bis[(2S)-2-ethylhexyl] benzene-1,2-dicarboxylate | 43.59 | 0.35|
| Scutellariae Radix       | MOL002879 | Diop                         | 43.59  | 0.39|
| Scutellariae Radix       | MOL002897 | Epiberberine                 | 43.09  | 0.78|
| Scutellariae Radix       | MOL002928 | Oroxyl a                     | 41.37  | 0.23|
| Scutellariae Radix       | MOL002914 | Eriodictol (flavanone)      | 41.35  | 0.24|
| Scutellariae Radix       | MOL002910 | Carthamidin                  | 41.15  | 0.24|
| Scutellariae Radix       | MOL002913 | Dihydrobasacalin_gt         | 40.04  | 0.21|
| Scutellariae Radix       | MOL000525 | Norwogonitin                 | 39.4   | 0.21|
| Scutellariae Radix       | MOL010415 | 11,13-Eicosadienoic acid, methyl ester | 39.28 | 0.23|
| Scutellariae Radix       | MOL002926 | Dihydrooroxyl A              | 38.72  | 0.23|
| Scutellariae Radix       | MOL012266 | Rivularin                    | 37.94  | 0.37|
| Scutellariae Radix       | MOL002908 | 5,8,2'-Trihydroxy-7-methoxyflavone | 37.01 | 0.27|
| Scutellariae Radix       | MOL002925 | 5,7,2',6'-Tetrahydroxyflavone | 37.01  | 0.24|
| Scutellariae Radix       | MOL000358 | beta-Sitosterol              | 36.91  | 0.75|
| Scutellariae Radix       | MOL000359 | Sitosterol                   | 36.91  | 0.75|
| Scutellariae Radix       | MOL012245 | 5,7,4'-Trihydroxy-6-methoxyflavanone | 36.63 | 0.27|
| Scutellariae Radix       | MOL002933 | 5,7,4'-Trihydroxy-8-methoxyflavone | 36.56 | 0.27|
| Scutellariae Radix       | MOL001689 | Acacetin                     | 34.97  | 0.24|
| Scutellariae Radix       | MOL002909 | 5,7,2,5-Tetrahydroxy-8,6-dimethoxyflavone | 33.82 | 0.45|
| Scutellariae Radix       | MOL001506 | Supraene                     | 33.55  | 0.42|
| Scutellariae Radix       | MOL002714 | Baicalin                     | 33.52  | 0.21|
| Scutellariae Radix       | MOL000552 | 5,2'-Dihydroxy-6,7,8-trimethoxyflavone | 31.71 | 0.35|
| Scutellariae Radix       | MOL000173 | Wogonin                      | 30.68  | 0.23|
| Scutellariae Radix       | MOL001458 | Coptisine                    | 30.67  | 0.86|
| Coptidis Rhizoma         | MOL002907 | Corchoroside A_qt           | 104.95 | 0.78|
| Coptidis Rhizoma         | MOL008647 | Moupinamide                  | 86.71  | 0.26|
| Coptidis Rhizoma         | MOL000785 | Palmatine                    | 64.6   | 0.65|
| Coptidis Rhizoma         | MOL000622 | Magnograndiolide            | 63.71  | 0.19|
| Coptidis Rhizoma         | MOL002903 | (R)-canadine                 | 55.37  | 0.77|
| Coptidis Rhizoma         | MOL000998 | Quercetin                    | 46.43  | 0.28|
| Coptidis Rhizoma         | MOL002668 | Worenine                     | 45.83  | 0.87|
| Coptidis Rhizoma         | MOL013352 | Obacunone                    | 43.29  | 0.77|
| Coptidis Rhizoma         | MOL002897 | Epiberberine                 | 43.09  | 0.78|
| Coptidis Rhizoma         | MOL001454 | Berberine                    | 36.86  | 0.78|
| Coptidis Rhizoma         | MOL002904 | Berberrubine                 | 36.68  | 0.82|
| Coptidis Rhizoma         | MOL002894 | Berberrubine                 | 35.74  | 0.73|
| Coptidis Rhizoma         | MOL000762 | Palmidin A                   | 35.36  | 0.65|
| Coptidis Rhizoma         | MOL001458 | Coptisine                    | 30.67  | 0.86|
| Glycyrrhiza Radix et Rhizoma | MOL002311 | Glycyrol                     | 90.78  | 0.67|
| Glycyrrhiza Radix et Rhizoma | MOL004990 | 7,2',4'-Trihydroxy-5-methoxy-3-arylcoumarin | 83.71 | 0.27|
Table 1: Continued.

| Chinese medicine        | Mol ID     | Molecule Name                                                                 | OB (%) | DL   |
|-------------------------|------------|------------------------------------------------------------------------------|--------|------|
| Glycyrrhiza Radix Et Rhizoma | MOL004904  | Licopyranocoumarin                                                           | 80.36  | 0.65 |
| Glycyrrhiza Radix Et Rhizoma | MOL004891  | Shinpterocarpin                                                             | 80.3   | 0.73 |
| Glycyrrhiza Radix Et Rhizoma | MOL005017  | Phaseol                                                                     | 78.77  | 0.58 |
| Glycyrrhiza Radix Et Rhizoma | MOL004841  | Licochalcone B                                                             | 76.76  | 0.19 |
| Glycyrrhiza Radix Et Rhizoma | MOL004810  | Glyasperin F                                                                | 75.84  | 0.54 |
| Glycyrrhiza Radix Et Rhizoma | MOL001484  | Inermine                                                                   | 75.18  | 0.54 |
| Glycyrrhiza Radix Et Rhizoma | MOL000500  | Vestitol                                                                   | 74.66  | 0.21 |
| Glycyrrhiza Radix Et Rhizoma | MOL005007  | Glyasperins M                                                              | 72.67  | 0.59 |
| Glycyrrhiza Radix Et Rhizoma | MOL004941  | (2R)-7-hydroxy-2-(4-hydroxyphenyl)chroman-4-one                              | 71.12  | 0.18 |
| Glycyrrhiza Radix Et Rhizoma | MOL004959  | 1-Methoxyphaseoliddin                                                     | 69.98  | 0.64 |
| Glycyrrhiza Radix Et Rhizoma | MOL000392  | Formononetin                                                              | 69.67  | 0.21 |
| Glycyrrhiza Radix Et Rhizoma | MOL004863  | 3-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-8-(3-methylbut-2-enyl)chromone        | 66.37  | 0.41 |
| Glycyrrhiza Radix Et Rhizoma | MOL004903  | Liquiritin                                                                 | 65.69  | 0.74 |
| Glycyrrhiza Radix Et Rhizoma | MOL004808  | Glyasperin B                                                                | 65.22  | 0.44 |
| Glycyrrhiza Radix Et Rhizoma | MOL004829  | Glepidotin B                                                                | 64.46  | 0.34 |
| Glycyrrhiza Radix Et Rhizoma | MOL004855  | Licoricone                                                                  | 63.58  | 0.47 |
| Glycyrrhiza Radix Et Rhizoma | MOL004914  | 1,3-Dihydroxy-8,9-dimethoxy-6-benzofurano [3,2-c]chromone                   | 62.9   | 0.53 |
| Glycyrrhiza Radix Et Rhizoma | MOL004835  | Glypallichalcone                                                           | 61.6   | 0.19 |
| Glycyrrhiza Radix Et Rhizoma | MOL004907  | Glyzaglabrin                                                              | 61.07  | 0.35 |
| Glycyrrhiza Radix Et Rhizoma | MOL005000  | Gancaonin G                                                              | 60.44  | 0.39 |
| Glycyrrhiza Radix Et Rhizoma | MOL004824  | (2S)-6-(2,4-dihydroxyphenyl)-2-(2-hydroxypropan-2-yl)-4-methoxy-2,3-dihydrofuro[3,2-g]chromen-7-one | 60.25  | 0.63 |
| Glycyrrhiza Radix Et Rhizoma | MOL004849  | 3-(2,4-Dihydroxyphenyl)-8-(1,1-dimethylprop-2-enyl)-7-hydroxy-5-methoxy-coumarin | 59.62  | 0.43 |
| Glycyrrhiza Radix Et Rhizoma | MOL004328  | Naringenin                                                                | 59.29  | 0.21 |
| Glycyrrhiza Radix Et Rhizoma | MOL005003  | Licoagrocarpin                                                            | 58.81  | 0.58 |
| Glycyrrhiza Radix Et Rhizoma | MOL004838  | 8-(6-Hydroxy-2-benzofuranyl)-2,2-dimethyl-5-chromenol                        | 58.44  | 0.38 |
| Glycyrrhiza Radix Et Rhizoma | MOL005012  | Licoagroisoflavone                                                          | 57.28  | 0.49 |
| Glycyrrhiza Radix Et Rhizoma | MOL000211  | Mairin                                                                     | 55.38  | 0.78 |
| Glycyrrhiza Radix Et Rhizoma | MOL005018  | Xambioona                                                                  | 54.85  | 0.87 |
| Glycyrrhiza Radix Et Rhizoma | MOL005020  | Dehydroglyasperins C                                                       | 53.82  | 0.37 |
Table 1: Continued.

| Chinese medicine                      | Mol ID      | Molecule Name                                      | OB (%) | DL  |
|--------------------------------------|-------------|----------------------------------------------------|--------|-----|
| Glycyrrhiza Radix Et Rhizoma         | MOL004993   | 8-Prenylated eriodictyol                            | 53.79  | 0.4 |
| Glycyrrhiza Radix Et Rhizoma         | MOL004908   | Glabridin                                          | 53.25  | 0.47|
| Glycyrrhiza Radix Et Rhizoma         | MOL004910   | Glabranin                                          | 52.9   | 0.31|
| Glycyrrhiza Radix Et Rhizoma         | MOL004879   | Glycyrin                                           | 52.61  | 0.47|
| Glycyrrhiza Radix Et Rhizoma         | MOL004912   | Glabrone                                           | 52.51  | 0.5 |
| Glycyrrhiza Radix Et Rhizoma         | MOL004885   | Licoisoflavanone                                   | 52.47  | 0.54|
| Glycyrrhiza Radix Et Rhizoma         | MOL003656   | Lupiwighteone                                      | 51.64  | 0.37|
| Glycyrrhiza Radix Et Rhizoma         | MOL004856   | Gancaonin A                                        | 51.08  | 0.4 |
| Glycyrrhiza Radix Et Rhizoma         | MOL000239   | Jaranol                                            | 50.83  | 0.29|
| Glycyrrhiza Radix Et Rhizoma         | MOL004820   | Kanzonols W                                        | 50.48  | 0.52|
| Glycyrrhiza Radix Et Rhizoma         | MOL005001   | Gancaonin H                                        | 50.1   | 0.78|
| Glycyrrhiza Radix Et Rhizoma         | MOL005016   | Odoratin                                           | 49.95  | 0.3 |
| Glycyrrhiza Radix Et Rhizoma         | MOL000354   | Isorhamnetin                                       | 49.6   | 0.31|
| Glycyrrhiza Radix Et Rhizoma         | MOL004848   | Licochalcone G                                     | 49.25  | 0.32|
| Glycyrrhiza Radix Et Rhizoma         | MOL002565   | Medicarpin                                         | 49.22  | 0.34|
| Glycyrrhiza Radix Et Rhizoma         | MOL004857   | Gancaonin B                                        | 48.79  | 0.45|
| Glycyrrhiza Radix Et Rhizoma         | MOL004827   | Semilicoisoflavone B                               | 48.78  | 0.55|
| Glycyrrhiza Radix Et Rhizoma         | MOL004913   | 1,3-Dihydroxy-9-methoxy-6-benzofuran-3-[3,2-c]chromenone | 48.14  | 0.43|
| Glycyrrhiza Radix Et Rhizoma         | MOL000417   | Calycosin                                          | 47.75  | 0.24|
| Glycyrrhiza Radix Et Rhizoma         | MOL004961   | Quercetin der.                                     | 46.45  | 0.33|
| Glycyrrhiza Radix Et Rhizoma         | MOL000098   | Quercetin                                          | 46.43  | 0.28|
| Glycyrrhiza Radix Et Rhizoma         | MOL004911   | Glabrene                                           | 46.27  | 0.44|
| Glycyrrhiza Radix Et Rhizoma         | MOL004898   | (E)-3-[3,4-dihydroxy-5-(3-methylbut-2-enyl)phenyl]-1-(2,4-dihydroxyphenyl) prop-2-en-1-one | 46.27  | 0.31|
| Glycyrrhiza Radix Et Rhizoma         | MOL004974   | 3′-Methoxyglabridin                                | 46.16  | 0.57|
| Glycyrrhiza Radix Et Rhizoma         | MOL004811   | Glysasperin C                                      | 45.56  | 0.4 |
| Glycyrrhiza Radix Et Rhizoma         | MOL004949   | Isolicoflavonol                                    | 45.17  | 0.42|
| Glycyrrhiza Radix Et Rhizoma         | MOL004828   | Glepidotin A                                       | 44.72  | 0.35|
| Glycyrrhiza Radix Et Rhizoma         | MOL004948   | Isoglycyrol                                        | 44.7   | 0.84|
| Glycyrrhiza Radix Et Rhizoma         | MOL004866   | 2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-6-(3-methylbut-2-enyl)chromone | 44.15  | 0.41|
| Chinese medicine | Mol ID      | Molecule Name                           | OB (%) | DL  |
|------------------|------------|-----------------------------------------|--------|-----|
| Glycyrrhiza Radix Et Rhizoma | MOL004966  | 3′-Hydroxy-4′-O-methylglabridin         | 43.71  | 0.57|
| Glycyrrhiza Radix Et Rhizoma | MOL004915  | Eurycaipin A                           | 43.28  | 0.37|
| Glycyrrhiza Radix Et Rhizoma | MOL003896  | 7-Methoxy-2-methyl isoflavone          | 42.56  | 0.2 |
| Glycyrrhiza Radix Et Rhizoma | MOL000422  | Kaempferol                              | 41.88  | 0.24|
| Glycyrrhiza Radix Et Rhizoma | MOL004883  | Licoisoflavone                         | 41.61  | 0.42|
| Glycyrrhiza Radix Et Rhizoma | MOL005008  | Glycyrrhiza flavonol A                 | 41.28  | 0.6 |
| Glycyrrhiza Radix Et Rhizoma | MOL005013  | 18α-Hydroxyglycyrrhetic acid           | 41.16  | 0.71|
| Glycyrrhiza Radix Et Rhizoma | MOL004924  | (−)-Medicocarpin                       | 40.99  | 0.95|
| Glycyrrhiza Radix Et Rhizoma | MOL000497  | Licochalcone a                         | 40.79  | 0.29|
| Glycyrrhiza Radix Et Rhizoma | MOL004980  | Inflacoumarin A                        | 39.71  | 0.33|
| Glycyrrhiza Radix Et Rhizoma | MOL004815  | (E)-1-(2,4-dihydroxyphenyl)-3-(2,2-dimethylchromen-6-yl)prop-2-en-1-one | 39.62  | 0.35|
| Glycyrrhiza Radix Et Rhizoma | MOL004989  | 6-Prenylated eriodictyol               | 39.22  | 0.41|
| Glycyrrhiza Radix Et Rhizoma | MOL004884  | Licoisoflavone B                       | 38.93  | 0.55|
| Glycyrrhiza Radix Et Rhizoma | MOL004991  | 7-Acetoxy-2-methylisoflavone           | 38.92  | 0.26|
| Glycyrrhiza Radix Et Rhizoma | MOL004957  | HMO                                    | 38.37  | 0.21|
| Glycyrrhiza Radix Et Rhizoma | MOL004917  | Glycyrrhizin                           | 37.25  | 0.79|
| Glycyrrhiza Radix Et Rhizoma | MOL000359  | Sitosterol                             | 36.91  | 0.75|
| Glycyrrhiza Radix Et Rhizoma | MOL004945  | (2S)-7-hydroxy-2-(4-hydroxyphenyl) 8-(3-methylbut-2-enyl)chroman-4-one | 36.57  | 0.32|
| Glycyrrhiza Radix Et Rhizoma | MOL004978  | 2-[(3R)-8,8-dimethyl-3,4-dihydro-2H-pyran-[6,5-f]chromen-3-y]-5-methoxyphenol | 36.21  | 0.52|
| Glycyrrhiza Radix Et Rhizoma | MOL004935  | Sigmoidin-B                           | 34.88  | 0.41|
| Glycyrrhiza Radix Et Rhizoma | MOL004905  | 3,22-Dihydroxy-11-oxo-delta(12)-oleanene-27-alpha-methoxycarbonyl-29-oic acid | 34.32  | 0.55|
| Glycyrrhiza Radix Et Rhizoma | MOL004882  | Licocoumarine                          | 33.21  | 0.36|
| Glycyrrhiza Radix Et Rhizoma | MOL004860  | Licorice glycoside E                   | 32.89  | 0.27|
| Glycyrrhiza Radix Et Rhizoma | MOL001792  | DFV                                    | 32.76  | 0.18|
| Glycyrrhiza Radix Et Rhizoma | MOL004988  | Kanzonol F                             | 32.47  | 0.89|
| Glycyrrhiza Radix Et Rhizoma | MOL004833  | Phaseolinisoflavan                     | 32.01  | 0.45|
| Glycyrrhiza Radix Et Rhizoma | MOL004814  | Isotrifoliol                           | 31.94  | 0.42|
| Glycyrrhiza Radix Et Rhizoma | MOL004805  | (2S)-2-[4-hydroxy-3-(3-methylbut-2-enyl)phenyl]-8,8-dimethyl-2,3-dihydropyran-[2,3-f]chromen-4-one | 31.79  | 0.72|
| Glycyrrhiza Radix Et Rhizoma | MOL004985  | Icos-5-enolic acid                     | 30.7   | 0.2 |
Table 1: Continued.

| Chinese medicine             | Mol ID      | Molecule Name                                         | OB (%) | DL   |
|------------------------------|-------------|-------------------------------------------------------|--------|------|
| Glycyrrhiza Radix Et Rhizoma | MOL004996   | Gadelaidic acid                                       | 30.7   | 0.2  |
| Glycyrrhiza Radix Et Rhizoma | MOL004864   | 5,7-Dihydroxy-3-(4-methoxyphenyl)-8-(3-methylbut-2-enyl)chromone | 30.49  | 0.41 |
| Glycyrrhiza Radix Et Rhizoma | MOL004806   | Euchrenone                                            | 30.29  | 0.57 |

Note. OB: oral bioavailability; DL: drug-likeness.

Figure 1: GD-active ingredients-potential targets-enzymes network. The purple triangle represents 4 Chinese herbal medicines, the blue circle represents the active ingredients in GD, the green hexagon represents lactase and sucrase, and the yellow diamond represents the targets.

Figure 2: Diarrhea-potential targets-lactase-sucrase network. Pink hexagons represent diseases, green octagons represent lactase and sucrase, and yellow diamonds represent potential targets. The connection between nodes indicates the corresponding relationship between the two.
Intestinal functional enzymes (including lactase and sucrase) are widely distributed in the intestinal mucosa and contents and participated in many important biological metabolic processes and material circulation of the intestinal tract, playing an important role in the digestion, absorption, growth, and development of nutrients in the body [29]. Intestinal microorganisms are the main source of intestinal functional enzymes. While they use the food in the host digestive tract to satisfy their own growth, they can also produce various enzymes, organic acids, and nutrients to assist the host in nutrient absorption and energy metabolism and regulate the balance of intestinal microorganisms, which is closely related to the physiology and pathology of the host [30]. The occurrence of diarrhea reduces the number of physiological bacteria and increases the conditional pathogenic bacteria. Changes in the composition and structure of intestinal microbes will also affect the activity of intestinal enzymes [31]. Some bacteria in the intestines, such as Bacteroides, Streptococcus, Lactobacillus, and Bifidobacterium, have excellent enzyme systems, which contribute to

4. Discussion

Figure 3: GD-active ingredients-enzymes-diarrhea network. The purple triangle represents 4 Chinese herbal medicines, the blue circle represents the active ingredients in GD, the green polygon represents lactase and sucrase, the pink polygon represents disease, and the yellow diamond represents the targets.
Table 2: Top 30 active ingredients or potential target proteins in the GD-active ingredient-enzyme-diarrhea network.

| Name             | DC  | BC  | CC  |
|------------------|-----|-----|-----|
| Quercetin        | 284 | 0.4742 | 0.4963 |
| PTGS2            | 122 | 0.0911 | 0.5218 |
| HSP90            | 95  | 0.0595 | 0.4845 |
| CALM             | 94  | 0.0230 | 0.3818 |
| AR               | 93  | 0.0352 | 0.4532 |
| ESR1             | 92  | 0.0205 | 0.3602 |
| NOS2             | 91  | 0.0187 | 0.3769 |
| GC               | 88  | 0.0512 | 0.4553 |
| PRSS1            | 79  | 0.0263 | 0.4386 |
| Formononetin     | 76  | 0.0389 | 0.3741 |
| PTGS1            | 76  | 0.0494 | 0.4678 |
| beta-Sitosterol  | 74  | 0.0366 | 0.3755 |
| PPARG            | 70  | 0.0276 | 0.4386 |
| SCN5A            | 69  | 0.0319 | 0.4266 |
| NCOA2            | 68  | 0.0367 | 0.4248 |
| CDK2             | 66  | 0.0065 | 0.3342 |
| PIM1             | 65  | 0.0050 | 0.3215 |
| F10              | 63  | 0.0139 | 0.4006 |
| ESR2             | 63  | 0.0049 | 0.3210 |
| GSK3B            | 62  | 0.0052 | 0.3282 |
| Kaempferol       | 58  | 0.0635 | 0.3884 |
| CHEK1            | 57  | 0.0049 | 0.3272 |
| CCNA2            | 55  | 0.0035 | 0.3160 |
| DPP4             | 52  | 0.0172 | 0.4136 |
| MAPK14           | 52  | 0.0037 | 0.3230 |
| Wogonin          | 45  | 0.0437 | 0.3769 |
| ADRB2            | 45  | 0.0184 | 0.4095 |
| RXRA             | 45  | 0.0150 | 0.4014 |
| 7-Methoxy-2-methyl isoflavone | 43  | 0.0178 | 0.3783 |
| F2               | 41  | 0.0093 | 0.3884 |

Note. DC: degree centrality; BC: betweenness centrality; CC: closeness centrality.

Promoted the recovery of lactase and sucrase activities in antibiotic-associated diarrhea mice [8, 36]. Previous studies indicated [21] that GD markedly reduced the microbial activity in the intestinal contents and intestinal mucosa of mice (p < 0.05; p < 0.05). The activities of lactase and sucrase in the intestinal contents were significantly decreased (p < 0.05; p < 0.05), the activities of lactase in the intestinal mucosa decreased (p < 0.05), and the activities of sucrase increased (p < 0.05). This might be due to the rich content of intestinal flora in intestinal contents, which had a two-way effect on the regulation of lactase and sucrase activities.

Combined with network pharmacological analysis, we constructed the GD-active ingredient-potential target-enzymes network. The analysis results adopted “DC,” “BC,” and “CC” to determine the key nodes and screened the active ingredients and targets according to the network median value ≥ median. The median degree of the active ingredient was 18, and the target degree was 2. Among them, quercetin, formononetin, beta-sitosterol, kaempferol, and wogonin were the main active ingredients screened out in the network, and PTGS2, HSP90, CALM, AR, and ESR1 were the main active targets, and both played an important role in the regulation of lactase and sucrase by GD. At the same time, according to the target information of diarrhea, lactase and sucrase, we constructed the diarrhea-potential target-enzyme network. In this network analysis, we indicated that HNF1A might play an important role in diarrhea affecting lactase and sucrase. Then, we used Cytoscape 3.7.2 software to construct the GD-active ingredient-enzyme-diarrhea network. The results showed that quercetin, formononetin, beta-sitosterol, kaempferol, and wogonin played an important role in the regulation of lactase and sucrase activity by GD in the treatment of diarrhea. Quercetin is one of the more important bioflavonoids found in current research [37, 38]. Quercetin affects the quantity and quality of the intestinal microbiota, thereby indirectly affecting their own metabolism and bioavailability [39]. Studies have indicated that quercetin can enhance the tolerance of diabetic animals to hyperglycemia and control the further development of diabetic complications by regulating the activity of lactase in the intestine of diabetic rats [40]. According to the results of in vitro experiments [41], quercetin significantly support the proliferation of Lactobacillus within a certain concentration range, and Lactobacillus contributes to the hydrolysis of intestinal enzymes. Some studies have reported that active ingredients such as formononetin and beta-sitosterol have certain anti-inflammatory effects. These anti-inflammatory effects can be achieved through the regulation of intestinal flora. Among them, formononetin achieve the anti-inflammatory effect by regulating intestinal flora in the process of diarrhea [42]. Beta-sitosterol treatment to intestinal epithelial cells significantly increases expression of antimicrobial peptides and reduces survival of intracellular Salmonella typhimurium [43]. Also, some bacteria in the intestine are involved in affecting the regulation of intestinal enzymes. It is inferred that these active ingredients may regulate intestinal enzyme activity by regulating some bacteria in the intestine, thus achieving the effect of treating diarrhea. On this basis, we also found that some ingredients in GD might...
act on multiple targets, while the phenomenon that different ingredients act on the same target together reflected the mechanism of interaction between multiple ingredients in TCM and multiple targets.

Molecular docking studies were carried out to confirm the interaction between active ingredients and diarrhea-related potential target at the molecular level. This determined the binding pose of the active ingredients when bound to the target protein and suggested that the active ingredients might have high binding affinity for proteins encoded by diarrhea-related genes. The results of this study showed that the combination of GD and diarrhea target binding energy was negative, indicating that there was binding activity between the ingredient and the target protein. Among these interactions, the most important node (formononetin) had the high affinity with potential target in the molecular docking score. This result indicated that instead of one ingredient interacting with one target protein, one or more ingredients interact with multiple target proteins. Based on this, it was speculated that these ingredients might play an important role in GD in regulating the expression of diarrhea target protein.

5. Conclusions

To sum up, the active ingredients in GD (such as quercetin, formononetin, and β-sitosterol) may enhance the microbial activity of the intestinal mucosa of diarrhea with IDHS mice and decrease the intestinal contents through multiple targets, so as to achieve the therapeutic effect of diarrhea, in order to provide the basis for the clinical diarrhea differentiation diagnosis and the mechanism research of the curative effect of TCM prescription. Simultaneously, there were still limitations in this study, i.e., the forecast results were obtained based on existing limited databases and might involve the existence of factors such as insufficient research on key targets of diarrhea, unknown chemical composition and structure of GD, and the interaction relationship between the ingredients. Additionally, this study only provides a preliminary hypothesis for the scientific study of TCM; animal experiments, molecular experiments, and clinical investigations should be performed to verify the mechanism of GD against diarrhea in future studies.

Abbreviations

IDHS: Intestinal damp-heat syndrome
FDA: Fluorescein diacetate
GD: Gegenqinlian decoction
PLR: Puerarie Lobatae Radix
SR: Scutellariae Radix
CR: Coptidis Rhizoma
GRER: Glycyrrhiza Radix Et Rhizoma
TCM: Traditional Chinese medicine
TCMSP: Traditional Chinese Medicine Systems Pharmacology
OB: Oral bioavailability
DL: Drug-likeness
UniProt: Universal protein
DC: Degree centrality
**Data Availability**

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

**Disclosure**

The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

**Conflicts of Interest**

The authors declare no conflicts of interest.

**Authors’ Contributions**

XY Li performed network analysis and drafted the manuscript; CY Zhang analyzed the data; and ZJ Tan and JL Yuan were responsible for studying the design and collecting fund. The decision to submit the manuscript for publication was made by all the authors. All authors read the manuscript for the final approved version.

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**References**

[1] S. S. Zhang, C. J. Wang, Y. F. Li, and N. Wang, "Expert consensus on diagnosis and treatment of diarrhea in Chinese medicine," *Journal of Traditional Chinese Medical Sciences*, vol. 58, pp. 1256–1260, 2017.

[2] Y. Zhao, Y. F. Zhao, J. H. Peng, Q. Feng, and Y. Y. Hu, "Thoughts on the relationship between damp-heat syndrome of chronic liver disease and intestinal microecology," *World Chinese Medicine*, vol. 14, pp. 1696–1700, 2019.

[3] P. F. Ding, J. X. Li, Y. Guo, T. Y. Mao, and X. J. Zhao, "Study on diversity of intestinal flora of patients with large damp heat syndrome and ulcerative colitis by high-throughput sequencing," *World Science and Technology-Modernization of Traditional Chinese Medicine*, vol. 20, no. 6, pp. 967–973, 2018.

[4] G. Wark, D. Samocha-Bonet, S. Ghaly, and M. Danta, "The role of diet in the pathogenesis and management of inflammatory bowel disease: a review," *Nutrients*, vol. 13, no. 1, p. 135, 2020.

[5] T. Zhoujin, W. Hai, L. Fulin et al., "Effect of ultra-micro powder qweibaishusan on the intestinal microbiota and enzyme activities in mice," *Acta Ecologica Sinica*, vol. 32, no. 21, pp. 6856–6863, 2012.

[6] H. Y. Hui, L. He, X. X. Peng et al., "The influence of antibiotics modeling on the intestinal lactase activity in dysbacteriotic diarrhea mice," *Chinese Journal of Preventive Veterinary Medicine*, vol. 39, no. 9, pp. 761–763, 2017.

[7] R. Hu, M. T. Zhang, and F. Tang, "Effect of Weichang'an pill on intestinal digestive ferment and the AQP4 concentration in proximal colon in IBS-D rats," *China Journal of Chinese Materia Medica*, vol. 35, no. 21, pp. 2899–2903, 2010.

[8] K. X. Guo, X. X. Peng, Y. N. Mao et al., "Effect of qweibai zhu san on intestinal sucrase activity in mice with diarrhea," *Chinese Journal of Microecology*, vol. 31, no. 10, pp. 1130–1134, 2019.

[9] Y. X. Xu, L. L. He, and Y. X. Liu, "Effects of biochar addition on enzyme activity and fertility in paddy soil after six years," *Chinese Journal of Applied Ecology*, vol. 30, no. 4, pp. 3770–3772, 2019.

[10] Y. Tang, Y. Wu, H. Y. Hui, and Z. J. Tan, "Effect of Tong-shiyao fang prescription on intestinal microbial activity in mice with Ganqi chenpi diarrhea," *Chinese Journal of Microecology*, vol. 32, no. 1, pp. 17–20, 2020.

[11] R. Swisher and G. C. Carroll, "Fluorescein diacetate hydrolysis as an estimator of microbial biomass on coniferous needle surfaces," *Microbial Ecology*, vol. 6, no. 3, pp. 217–226, 1980.

[12] Z. X. Bian, H. Y. Qin, S. L. Tian, and S. D. Qi, "Combined effect of early life stress and acute stress on colonic sensory and motor responses through serotonin pathways: differences between proximal and distal colon in rats," *Stress (Amsterdam, Netherlands)*, vol. 14, no. 4, pp. 448–458, 2011.

[13] X. J. Xiong, "Gegen Qinlian Decoction formula syndrome and its application for diabetes, hypertention, hyperlipidemia, and obesity," *China Journal of Chinese Materia Medica*, vol. 45, no. 12, pp. 2760–2764, 2019.

[14] H. Y. Li, L. H. Zhao, B. Zhang et al., "A network pharmacology approach to determine active compounds and action mechanisms of ge-gen-qin-lian decoction for treatment of type 2 diabetes," *Evidence-Based Complementary and Alternative Medicine*, vol. 2014, Article ID 495840, 12 pages, 2014.

[15] X. G. Feng, Y. Z. Yan, Y. P. Zeng, and Y. F. Guo, "The effect of gegen qianlian decoction on intestinal flora damp-heat syndrome of type 2 diabetes," *World Journal of Integrated Traditional and Western Medicine*, vol. 11, no. 8, pp. 1110–1112, 2016.

[16] Y. Chen, J. Lu, S. M. Zhu et al., "Effect of gegen qinlian decoction and it’s different compatibility groups on gut microbiota in rats with acute enteritis based on high-throughput sequencing," *Chinese Journal of Traditional Chinese Medicine*, vol. 45, no. 6, pp. 1406–1417, 2019.

[17] X. G. Shi, J. X. Shi, and H. T. Liu, "Effects of buzhong yiqi decoction (BZYQ) on SGLT1/NHE3 pathway in rats with spleen deficient diarrhea," *Traditional Chinese Medicine and Clinical Pharmacology*, vol. 29, no. 1, pp. 8–12, 2018.

[18] Y. S. He, Y. Tang, Y. F. Xiao, N. Q. Xiao, and H. Y. Hui, "Effects of gegen qianlian decoction on microbial growth in simulated gastric and intestinal liquid," *Chinese Journal of Microecology*, vol. 32, no. 2, pp. 125–137, 2020.

[19] J. Liu, Y. Li, Y. Zhang et al., "A network pharmacology approach to explore the mechanisms of qishen granules in heart failure," *Medical Science Monitor*, vol. 25, pp. 7735–7745, 2019.

[20] S. Li and B. Zhang, "Traditional chinese medicine network pharmacology: theory, methodology and application," *Chinese Journal of Natural Medicines*, vol. 11, no. 2, pp. 110–120, 2013.

[21] H. Y. Hui, Y. S. He, Y. C. Luo, and Z. J. Tan, "Effect of ge-gen-qin-lian decoction on intestinal microbial activity and enzyme activity in diarrhea mice with intestinal dampness-heat
syndrome,” *Chinese Journal of Applied & Environmental Biology*, vol. 26, no. 6, p. 26, 2020.

[22] J. Ru, P. Li, J. Wang et al., “TCMSP: a database of systems pharmacology for drug discovery from herbal medicines,” *Journal of Cheminformatics*, vol. 6, no. 1, pp. 13–16, 2014.

[23] L. P. Liu, X. Long, X. S. Cao, X. Y. Xu, Y. W. Luo, and R. Gui, “Research on active compounds of maxingyigang decoction for treatment of coronavirus disease 2019 based on network pharmacology and molecular docking,” *Chinese Traditional and Herbal Drugs*, vol. 51, no. 7, pp. 1741–1749, 2020.

[24] X. Guo, J. Ji, Z. Feng, X. Hou, Y. Luo, and Z. Mei, “A network pharmacology approach to explore the potential targets underlying the effect of sinomenine on rheumatoid arthritis,” *International Immunopharmacology*, vol. 80, pp. 106201–115769, 2020.

[25] X. Du, L. Zhao, Y. Yang et al., “Investigation of the mechanism of action of Porana sinensis hems against gout arthritis using network pharmacology and experimental validation,” *Journal of Ethnopharmacology*, vol. 252, pp. 112606–118741, 2020.

[26] M. Franz, C. T. Lopes, G. Huck et al., “A graph theory library for visualisation and analysis,” *Bioinformatics*, vol. 32, pp. 309–311, 2016.

[27] D. S. Goodsell, G. Zardecki, L. Di Costanzo et al., “RCSB protein data bank: enabling biomedical research and drug discovery,” *Protein Science*, vol. 29, no. 1, pp. 52–65, 2020.

[28] T. Sterling and J. J. Irwin, “Zinc 15-ligand discovery for everyon,” *Journal of Chemical Information and Modeling*, vol. 55, no. 11, pp. 2324–2337, 2015.

[29] J. F. Chen and X. Y. Qu, “Effects of montmorillonite and Bacillus subtilis on plasma biochemical indexes, small intestinal brush edge enzyme activity and mucin expression in layers,” *Chinese Journal of Animal Science*, vol. 56, no. 9, pp. 1–10, 2020.

[30] Y. S. He, Z. J. Tan, D. D. Li, and H. Y. Hui, “Effect of bao-he pills on intestinal microorganisms and enzyme activity in mice with dyspepsia,” *Chinese Journal of Microecology*, vol. 31, no. 7, pp. 763–767, 2019.

[31] S. J. Guo, D. J. Jiang, Z. L. Li, Q. Zhang, and L. Zhang, “Research progress on relationship between intestinal flora and common gastrointestinal diseases and treatments of Chinese materia medica and microecological preparations,” *Chinese Traditional and Herbal Drugs*, vol. 49, no. 18, pp. 4424–4431, 2018.

[32] C.-X. Long, Y.-F. Guo, Y.-W. Liu, X.-X. Peng, and Z.-J. Tan, “Immunoprotective effect of traditional chinese medicine on intestinal mucosa,” *World Chinese Journal of Digestology*, vol. 25, no. 35, pp. 3115–3122, 2017.

[33] L. He, C. X. Long, Y. J. Liu, H. Y. Hui, and Z. J. Tan, “Research progress on microorganism lactase,” *Journal of the Food and Fermentation Industry*, vol. 11, no. 8, Article ID e0160488, 2017.

[34] A. M. Neyrinck, B. Pachikian, B. Tamiaiu et al., “Intestinal sucrase as a novel target contributing to the regulation of glycemia by prebiotics,” *PLoS One*, vol. 11, no. 8, Article ID e0160488, 2016.

[35] H. Y. Hui, M. J. Peng, N. Q. Xiao, and D. D. Li, “The effect of modeling dysbacterial diarrhea with antibiotics on molecular diversity of intestinal microbiota in mice,” *Chinese Journal of Microecology*, vol. 30, no. 9, pp. 1016–1019, 2018.

[36] H. Y. Hui, K. J. Shen, D. D. Li, and Z. J. Tan, “Influence of qiwei baizhu powder on the lactase activity in intestine of mice with diarrhea induced by antibiotics,” *Chinese Journal of Microecology*, vol. 30, no. 10, pp. 1126–1129, 2018.