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ORIGINAL ARTICLE

Screening compounds for treating the diabetes and COVID-19 from Miao medicine by molecular docking and bioinformatics

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Angiotensin-converting enzyme II;
Dipeptidyl peptidase 4

Abstract Both diabetes and Corona Virus Disease 2019 (COVID-19) are seriously harmful to human health, and they are closely related. It is of great significance to find drugs that can simultaneously treat diabetes and COVID-19. Based on the theory of traditional Chinese medicine for treating COVID-19, this study first sorted out the compounds of Guizhou Miao medicine with "return to the lung channel" and "clear heat and detoxify" effects in China. The active components against COVID-19 were screened by molecular docking with SARS-CoV-2 PLpro and angiotensin-converting enzyme II as targets. Furthermore, the common target dipeptidyl peptidase 4 (DPP4) of diabetes and COVID-19 was used as a screening protein, and molecular docking was used to obtain potential components for the treatment of diabetes and COVID-19. Finally, the mechanism of potential ingredients in the treatment of diabetes and COVID-19 was explored with bioinformatics. More than 80 kinds of Miao medicine were obtained, and 584 compounds were obtained. Further, 110 compounds against COVID-19 were screened, and top 6 potential ingredients for the treatment of diabetes and COVID-19 were screened, including 3-O-β-D-Xylopyranosyl-(1-6)-β-D-glucopyranosyl-(1-6)-β-D-glucopyranosyl oleanolic acid 28-O-β-D-glucopyranosyl ester, Glycyrrhizic acid, Sequoiaflavone, 2-O-Caffeoyl maslinic acid, Pholidotin, and Ambewelamide A. Bioinformatics analysis found that their mechanism of action in treating diabetes and COVID-19 may be related to regulating the expression of DPP4, angiotensin II type 1 receptor, vitamin D receptor, plasminogen, chemokine C–C-motif receptor 6, and interleukin 2. We believe that Guizhou Miao medicine is rich in potential ingredients for the treatment of diabetes and COVID-19.

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1. Introduction

Diabetes is a metabolic disease characterized by hyperglycemia caused by insulin secretion defect and/or its biological function obstacle, which seriously affects human health and quality of life (Chatterjee et al., 2017). Diabetes also brings heavy mental and economic burden to the family of patients and society (He et al., 2021). The International diabetes Federation predicts that by 2040, the number of diabetes patients worldwide will reach 642 million, with an average of one diabetes patient dying every 6 s (Ogurtsova et al., 2017). The search for safe and effective drugs for the treatment of diabetes has been a hot topic of research. Modern research has found that chronic disease diabetes is closely related to many diseases. When two or more critical illnesses are present at the same time, there are enormous challenges to the health and life of the patient. With the spread of SARS-CoV-2 novel coronavirus, more than 200 million people have been infected worldwide (Camporota et al., 2022). The clinical study found that Corona Virus Disease 2019 (COVID-19) will lead to the abnormal regulation of glucose metabolism, and the presence of diabetes is closely related to the severity of COVID-19. That is, there is a linkage effect between diabetes and COVID-19 (Huang et al., 2020). Recent studies have found that dipeptidyl peptidase 4 (DPP4) is a common target for the treatment of diabetes and COVID-19 (Alomair et al., 2022). For those diabetic patients with COVID-19 and those with abnormal glucose metabolism due to COVID-19, it is particularly important to find drugs with good affinity for DPP4 to fight against diabetes and COVID-19 at the same time.

Finding active ingredients from medicinal plants has always been a classic way to discover innovative drugs. Guizhou of China is rich in Miao medicine resources, which contains many active ingredients with anti-diabetic, anti-inflammatory and antiviral activity (Guo et al., 2006; Xu et al, 2020; Xu et al., 2022). It is of great value to find compounds with good affinity to DPP4 from Miao medicines in Guizhou. Molecular docking technology is a method that uses mathematical, biological and computer models to predict the affinity of small molecules to specific receptors (Boittier et al., 2020). Compared with cell and animal experimental screening, molecular docking technology has the advantages of rapidity, high accuracy and low cost, and can be used for large-scale screening of compounds. At present, there have been a large number of literature reports on drug screening for COVID-19, mainly including screening active compounds from the effective traditional Chinese medicine prescriptions and single herb for treating COVID-19, Traditional Chinese Medicine database, marine active peptides, Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP), and DrugBank database.

In this study, we first sorted out the medicinal plants with "return to the lung channel" and "clear heat and detoxify" effects commonly used by the Miao people in Guizhou of China, and the compounds from these Miao medicines were obtained according the literature reports and databases (Xu et al., 2020). The molecular docking technology was used to screen the small molecular components with good affinity with the potential targets SARS-CoV-2 3CL hydrolase protein (Mpro) and angiotensin-converting enzyme II (ACE2) for treating COVID-19. In all, a special small molecular library of Miao medicines against COVID-19 were built. Further, molecular docking technology was used to screen compounds with good affinity for DPP4 to fight against diabetes and COVID-19 at the same time from the special small molecular library of Miao medicines against COVID-19. Finally, the relationship between the core targets and potential compounds was explored with bioinformatics, and performing the molecular docking verification, so as to provide reference for the discovery of innovative drugs for treating the diabetes and COVID-19. The scheme of work is illustrated in Fig. 1.

2. Material and methods

2.1. The compounds from Miao medicines with "return to the lung channel" and "clear heat and detoxify"

Based on the 2003 edition of Guizhou Quality Standards for

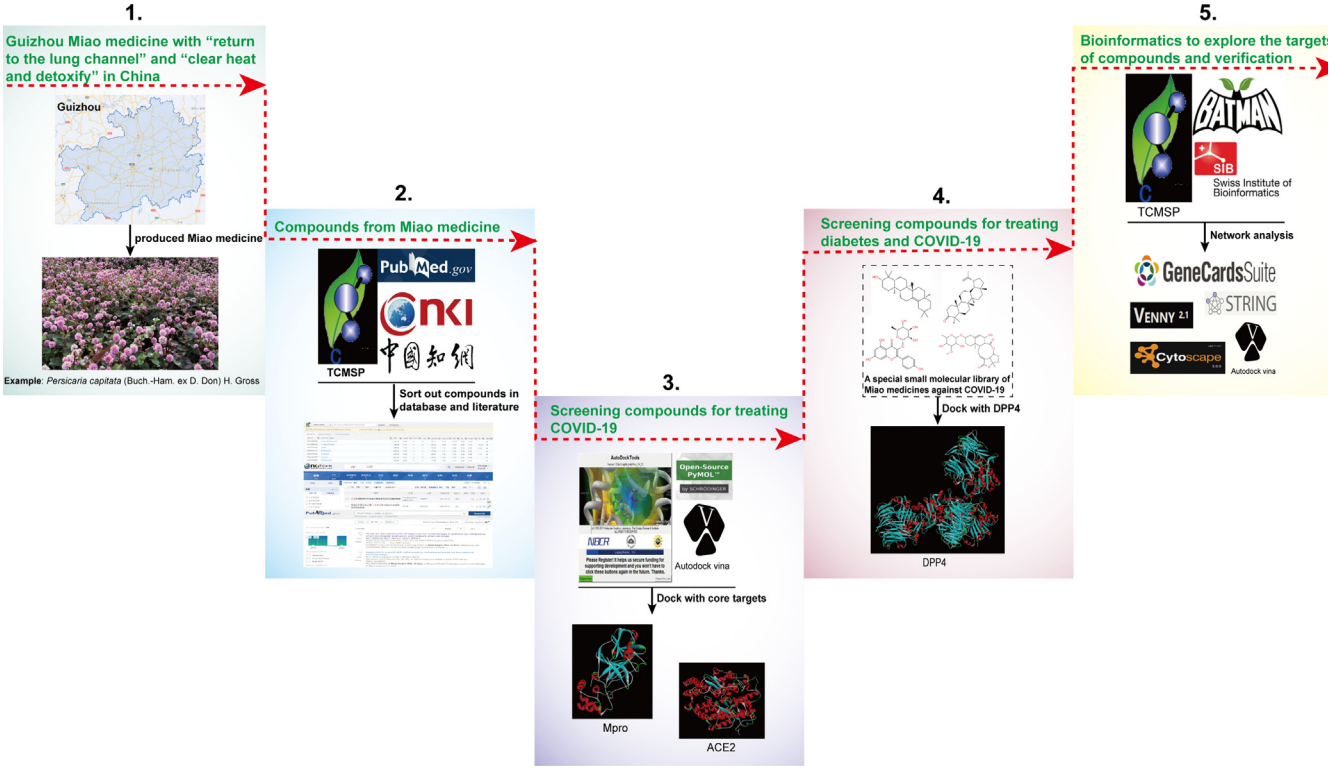


Fig. 1 The scheme of work.

Traditional and Ethnic Chinese Medicinal Materials and the Chinese Materia Medica – Miao Medicine Volume, we obtained the Miao medicines with "return to the lung channel" and "clear heat and detoxify" effects. The compounds from Miao medicines with "return to the lung channel" and "clear heat and detoxify" effects were sorted through the TCMSP (https://tcmspw.com/tcmsp.php) query and literature collation. Considering that compounds included in TCMSP have been used for molecular docking screening against COVID-19 (Liu et al., 2020), many special compounds not included in TCMSP database were selected for screening in this study.

2.2. A special small molecular library of Miao medicines against COVID-19 screened by Mpro and ACE2 as targets

The structural formula of compounds was downloaded from PubMed database (https://www.ncbi.nlm.nih.gov/) and convert the compound format to *pdbqt format using AutoDock 4.2. The *PDB format of Mpro (PDB ID: 6LU7) and ACE2 (PDB ID: 1R4L) was obtained from the PDB protein database (https://www.rcsb.org/), and PyMol software was applied to dehydrate and hydrogenate the proteins, and then AutoDock Vina software was used to convert the target protein format to *pdbqt format, optimizing the docking box size and docking coordinates, performing docking separately. The docking results were analyzed and visualized using PyMol software and Discovery Studio Visualizer.

2.3. Compounds for treating diabetes and COVID-19 screened by DPP4 as target

The structural formulae of the compounds were downloaded from the PubChem Compound database. The 3D structure of DPP4 (PDB ID: 2ONC) was downloaded from the PDB protein database in *PDB format, the protein was dehydrated and hydrogenated using PyMol software. The compound and target protein formats were converted to *pdbqt format using AutoDock software, the docking coordinates and box size were optimized, and then docking was performed separately using AutoDock Vina software, and the PyMol software and Discovery Studio Visualizer were used to visualize the docking results and to screen the compounds with good affinity.

2.4. Combining bioinformatics to explore the core targets of compounds for the treatment of diabetes and COVID-19 linkage

The targets of compounds were obtained from the TCMSP analysis platform, BATMAN-TCM (https://bionet.ncpsb.org/batman-tcm/) and Swiss Target Prediction database (https://www.swisstargetprediction.ch/). The diabetes and COVID-19-linked targets were screened by GeneCards database (https://www.genecards.org/). Venn's diagram was obtained by Venny (https://bioinfogp.cnb.csic.es/tools/venny/index. html), and identified common core targets for each potential component linked to diabetes and COVID-19 using Cytoscape software. The core targets of potential compounds for the treatment of diabetes and COVID-19 linkage and DPP4 were imported into STRING database (https://cn.string-db.org/), and the population was selected as human for the construction and analysis of protein interaction network, and Cytoscape software was applied for the presentation.

2.5. Molecular docking studies of potential compounds to core targets

Structural formulae of compounds were downloaded from the PubChem Compound database. The 3D structures of AGTR1 (PDB ID: 6OS2), VDR (PDB ID: 1IE9), PLG (PDB ID: 1KRN), CCR6 (PDB ID: 6WWZ) and IL2 (PDB ID: 1M48) were downloaded from the PDB protein database in *PDB format, and the proteins were dehydrated and hydrogenated using PyMol software, and the compounds and target protein formats were converted to *pdbqt format using AutoDock software to optimize the docking coordinates and box size, and then AutoDock Vina software for docking respectively.

3. Results

3.1. Results of collating compounds from Miao medicines with "return to the lung channel" and "clear heat and detoxify"

Finally, more than 80 kinds of Miao medicines with "return to the lung channel" and "clear heat and detoxify" effects were obtained, including *Emilia sonchifolia* (L.) DC., *Peristrophe japonica* (Thunb.) Bremek., *Bidens pilosa* L., root of *Chimonan thns* Praecox (L.) Link, *Hemsleya chinensis* Cogn. ex Forbes et Hemsl., *Ilex rotunda* Thunb., root of *Cyrtomium fortunei* J. Sm., *Stephania cepharantha* Hayata, and Leaf of *Hibiscus mutabilis* L.. Clinically, these Miao medicines with "return to the lung channel" and "clear heat and detoxify" effects are commonly used to treat pneumonia, cough, fever, sore throat, upper respiratory tract infections, and influenza, and are worthy of attention. Through the TCMSP database and literature collation, we obtained 584 compounds, and these components are mostly identified from Miao medicine in recent years. The classes of these components were mainly flavonoids, anthraquinones, alkaloids, terpenoids, saponins, phenols, and phenylpropanoids, among which the number of flavonoids and phenylpropanoids is higher. Typical Miao medicines and typical compounds in Miao medicine are shown in Fig. 2.

3.2. Screening results of active compounds against COVID-19

Using Mpro and ACE2 as targets, 198 compounds with good affinity for Mpro (Affinity value ≤ -7.5 kcal/mol) and 187 compounds with good affinity for ACE2 (Affinity value ≤ -9.3 kcal/mol) were found, which were comparable to positive reference drugs such as raltegravir, ritonavir, lopinavir and nirmatrelvir. The affinity of the compounds with Mpro and ACE2 was taken into account and the screened 110 active compounds have the potential to be developed as new drugs for the treatment of COVID-19, and deserve further study (Table 1). The virtual screening results between typical compounds and screening targets are shown in Fig. 3.

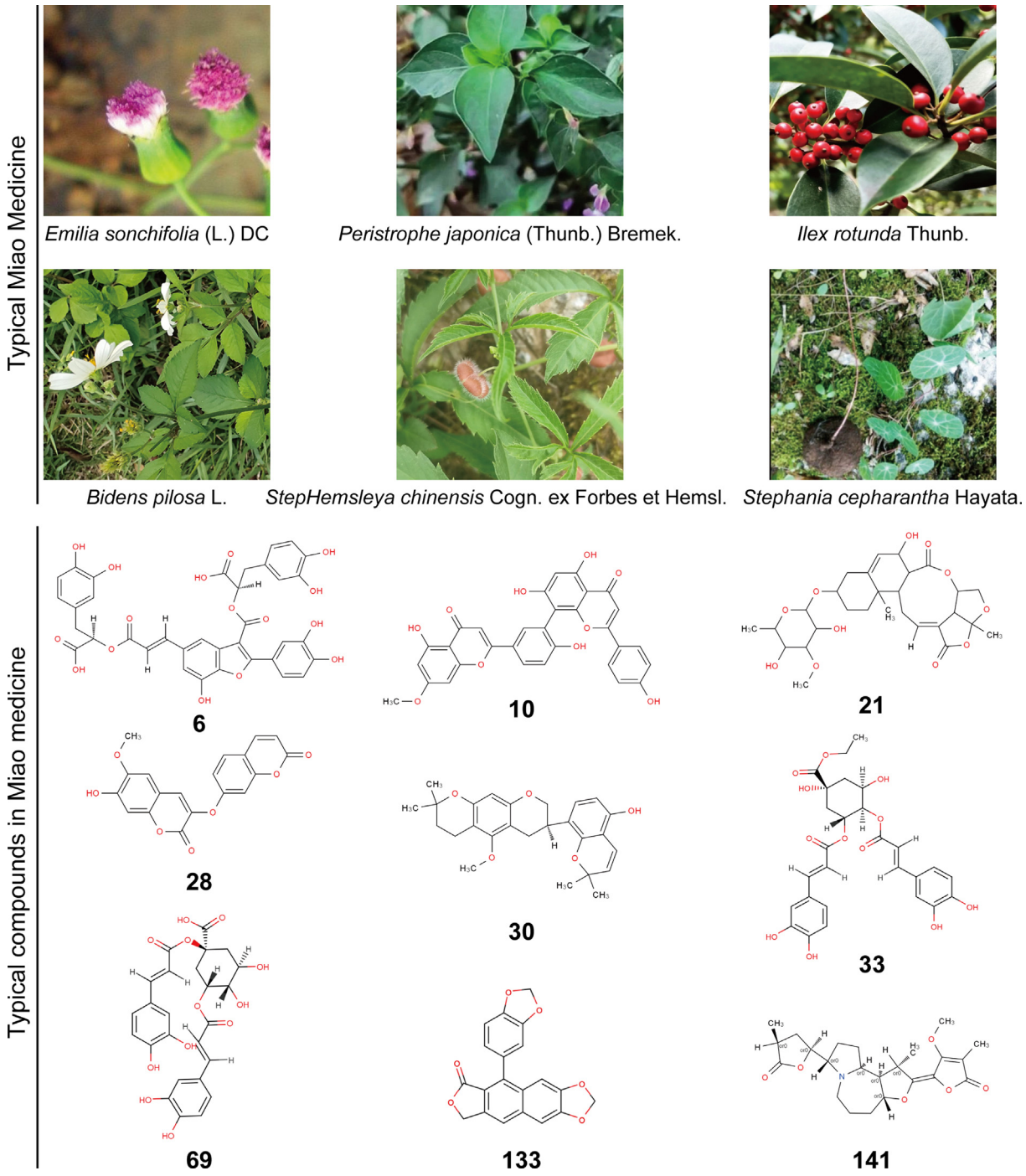


Fig. 2 Typical Miao medicines and typical compounds in Miao medicine.

3.3. Screening results of compounds for treating diabetes and COVID-19

Based on the target DPP4, a common target of COVID-19 and diabetes, 81 compounds with affinity values ≤ -9.2 kcal/mol with DPP4 were screened from the special small molecular library of Miao medicines against COVID-19. Among them, compounds **1**, **9**, **10**, **17**, **18** and **19** with better affinity than the positive control drug sitagliptin were screened, suggesting that these compounds may be used to treat diabetes and COVID-19 (Table 1, Fig. 4).

3.4. Protein interaction network analysis of potential components

Except the screening target DPP4, the Venn diagrams revealed that compounds **1**, **9**, **10**, **17**, **18** and **19** exert anti-diabetes and anti-COVID-19 activities through other targets (Fig. 5). The targets of the potential compounds were imported into

Table 1 Compounds of Miao medicine with good affinity to SARS-CoV-2 3CL hydrolase protein (Mpro), angiotensin-converting enzyme II (ACE2) and dipeptidyl peptidase 4 (DPP4).

No.	Compunds	Affinity with Mpro (kcal/mol)	Affinity with ACE2 (kcal/mol)	Affinity with DPP4 (kcal/mol)
1	3-O-β-D-Xylopyranosyl-(1-6)-β-D-glucopyranosyl-(1-6)-β-D-glucopyranosyl oleanolic acid 28-O-β-D-glucopyranosyl ester	−8.2	–	−10.7
2	Bulbocodin [bibenzyl]	−9.4	−11.1	–
3	Lithospermic acid B	–	−11.5	–
4	1,2,3,6-Tetragalloylglucose	–	−11.4	–
5	Datuarmeteloside B	−9	−10.8	–
6	Schizotenuin A	−8.6	−11.4	–
7	Pentagalloylglucose	−8.1	−11.3	–
8	Afzelin	−8.6	–	–
9	Glycyrrhizic acid	–	–	−10.7
10	Sequoiaflavone	−9.7	−11	−10.6
11	Echinuline	−8.2	−11.1	–
12	Licorice glycoside A	–	−11.1	–
13	Kaempferol-3-O-(2′,6′-digalloyl)-β-D-glucoside	−8.3	−11	–
14	Mudanpioside H	−8.1	−11	–
15	Schaftoside	–	−11	–
16	2′′-O-Galloylquercitrin	−8.6	–	–
17	2-O-Caffeoyl maslinic acid	–	–	−10.4
18	Ambewelamide A	–	−10.5	−10.3
19	Pholidotin	–	−10.9	−10.3
20	3-O-(2-Rhamnosylglucosyl) oleanolic acid	−8.4	–	−10.2
21	Neocynaversicoside	−8.2	−10.5	−10.2
22	Dibothrioclinin II	−8.7	–	−10.1
23	Inoscavin A	–	−10.7	−10.1
24	Cynatratoside A	–	−10.6	−10
25	Kanzonol E	−8.3	−12	−10
26	Isoacteoside	−8.5	−10.9	–
27	Cynaroside	−8.5	−10.3	–
28	Daphnoretin	−8.5	–	–
29	Viscumneoside III	−8.1	−10.9	–
30	Kanzonol J	−8.4	−10.6	–
31	(-)-Catechin gallate	−8.4	−10.5	–
32	11-O-Galloylbergenin	−8.4	−10.4	–
33	Ethyl 3,5-di-O-caffeoylquinate	−8.4	–	–
34	3,5-Dicaffeoylquinic acid	−8.4	–	–
35	Chrysophanol-1-O-β-gentiobioside	−8.4	–	–
36	Justicidin D	−8.4	−10.3	–
37	Kaempferol-7-O-rhamnoside	−8.4	−10.4	–
38	Neoharringonine	−8.4	−10.6	–
39	Kanzonol S	−8.3	−10.2	–
40	3-Galloyl-epicatechin	−8.3	−10.3	–
41	Calceolarioside B	−8.3	−10.1	–
42	Kaempferol-3-O-β-D-glucoside	−8.3	–	–
43	Pavetannin A	−8.3	–	–
44	Racemosol	−8.3	−10.2	–
45	Rutin	−8.3	–	–
46	Withaferin A	−8.3	−10.6	–
47	Cassameridine	−8.3	−10.6	–
48	Withanolide D	−8.1	−10.6	–
49	Atratoglaucoside A	−8.2	−10.4	−9.9
50	Glaucoside A	–	−10.6	−9.9
51	Kanzonol Z	−8.1	−10.3	−9.9
52	β-Amyrin	–	–	−9.8
53	Celastrol	–	–	−9.8
54	β-Amyrin acetate	–	–	−9.8
55	Olibanumol L	−8.1	–	−9.8
56	Urs-12-en-28-ol	–	–	−9.8
57	11-Deoxoglycyrrhetinic acid	–	–	−9.7
58	24-hydroxychiisanogenin	–	–	−9.7
59	4′-Demethylepipodophyllotoxin	–	−10.2	−9.7
60	Euglobal VII	–	–	−9.7

(*continued on next page*)

Table 1 (*continued*)

No.	Compunds	Affinity with Mpro (kcal/mol)	Affinity with ACE2 (kcal/mol)	Affinity with DPP4 (kcal/mol)
61	Isogomphrenin II	−8.6	−10.7	−9.7
62	Justicidin E	−8.4	−11.4	−9.7
63	Kanzonol F	–	–	−9.7
64	Lupenone	–	−10.3	−9.7
65	Oleanolic acid-28-O-β-D-glucopyranoside	−8.2	–	−9.7
66	Olibanumol G	–	–	−9.7
67	Hydnocarpin	−8.8	−10.4	−9.7
68	Ursolic acid	–	–	−9.7
69	1,3-Dicaffeoylquinic acid	−8.9	–	−9.6
70	2-Hydroxydiplopterol	–	–	−9.6
71	3,4-Dicaffeoylquinic acid	−9.1	−10.9	−9.6
72	3-β-O-(*trans*-p-Coumaroyl) maslinic acid	–	–	−9.6
73	α-Amyrin	–	–	−9.6
74	Isorhoifolin	–	−11.2	−9.6
75	Aurantiamide	–	–	−9.6
76	Glaucogenin C	–	−10.3	−9.6
77	Glochidiol	–	–	−9.6
78	Glutinone	–	–	−9.6
79	Isoneorautenol	–	–	−9.6
80	Bulbocodin D	−8.2	−10.5	–
81	Homoharringtonine	–	−10.5	–
82	Justicidin B	–	−10.5	–
83	Shanciguol	–	−10.5	–
84	Alnusonol	–	−10.4	–
85	Isosakuranin	−8.1	−10.4	–
86	Smiglaside C	–	−10.4	–
87	25-O-Acetylcimigenol	–	−10.3	–
88	Justicidin A	–	−10.3	–
89	Luteolin 7-O-glucuronide	–	−10.3	–
90	Tuberostemonine C	–	−10.3	–
91	Anhydroharringtonine	−8.5	−10.6	−9.5
92	18-β-Glycyrrhetinic acid	–	–	−9.5
93	Bulbocodin C	−8.4	−10.1	−9.5
94	Chilenine	–	–	−9.5
95	Corosolic acid	–	–	−9.5
96	3-epi-Maslinic acid	–	–	−9.5
97	Isogarcinol	–	−11.3	−9.5
98	Kanzonol V	−8.3	−10.6	−9.5
99	Olibanumol I	–	–	−9.5
100	Ursolic acid lactone	−8.7	–	−9.5
101	Kanzonol O	−8.2	–	–
102	Antofine	−8.2	–	–
103	Kaempferol 3-neohesperidoside	−8.2	–	–
104	Isoquercitrin	−8.2	–	–
105	Lanceoloside A	−8.1	–	–
106	3-O-β-D-Glucopyranosyl betulinic acid-28-O-β-D-glucopyranosyl-(1-6)-β-D-glucopyranoside	–	–	−9.4
107	Hydnocarpin D	−8.1	−10.2	−9.4
108	Luteolin 4′-O-glucoside	−8.3	–	−9.4
109	Macranthoin G	−8.3	–	−9.4
110	Pristimerin	–	–	−9.4
111	Taraxacerin	–	–	−9.4
112	17-epi-Lupenylacetate	–	–	−9.3
113	Ethyl 3,4-dicaffeoylquinate	–	–	−9.3
114	3-Hydroxynorlupen-2-one	–	–	−9.3
115	3-O-galloylprocyanidin B-3	−8.5	–	−9.3
116	Chiisanogenin	–	–	−9.3
117	Chrysophanein	−8.1	−10.1	−9.3
118	Hyperinol B	−8.6	–	−9.3
119	Kanzonol K	–	–	−9.3
120	Lupeol acetate	–	–	−9.3
121	Olibanumol E	–	–	−9.3

Table 1 (*continued*)

No.	Compunds	Affinity with Mpro (kcal/mol)	Affinity with ACE2 (kcal/mol)	Affinity with DPP4 (kcal/mol)
122	Olibanumol M	–	–	−9.3
123	Pleionesin C	−8.2	–	−9.3
124	Quercetin 3-O-robibioside	−8.3	−10.6	−9.3
125	Sampsonione N	–	−10.6	−9.3
126	4-O-Galloylbergenin	–	−10.3	−9.2
127	Cichoric acid	–	–	−9.2
128	Kanzonol H	−8.2	–	−9.2
129	Lupeol	–	–	−9.2
130	Betulinic Acid	–	−10.5	−9.2
131	Picene	–	−10.6	−9.2
132	Salvin B	–	–	−9.2
133	Taiwanin C	−8.3	−11.4	−9.2
134	(+)-Epiexcelsin	–	−10.2	–
135	Allocrypopine	–	−10.2	–
136	Isoharringtonine	–	−10.2	–
137	Justicidin C	–	−10.2	–
138	Kanzonol C	–	−10.2	–
139	Alphitolic acid	–	−10.1	–
140	Harringtonine	–	−10.1	–
141	Isoprotostemonine	–	−10.1	–
142	Kaempferol-3-O-β-D-rutinoside	–	−10.1	–
143	Quercetin 3-O-β-D-glucoside	–	−10.1	–
144	Kanzonol G	–	−10.1	–
145	positive control 1 (raltegravir)	−7.9	−11	–
146	positive control 2 (ritonavir)	−8.7	−10	–
147	positive control 3 (lopinavir)	−8.8	−10.6	–
148	positive control 4 (nirmatrelvir)	−8.4	−10	–
149	positive control 5 (gemigliptin)	–	–	−9.2
150	positive control 6 (sitagliptin)	–	–	−10.2
151	positive control 7 (teneligliptin)	–	–	−9.2

"–": Less affinity with Mpro, ACE2 and DPP4 than positive control raltegravir or ritonavir or gemigliptin.

STRING database to obtain the PPI protein interaction network, and it was found that the targets were associated with each other, among which the closer relationship was found between DPP4, plasminogen (PLG) and angiotensin II type 1 receptor (AGTR1) (Fig. 6a). The association between potential components and targets is shown in Fig. 6b. Further, studies have reported that DPP4, PLG, AGTR1, vitamin D receptor (VDR), interleukin 2 (IL2) and chemokine C–C-motif receptor 6 (GPR29/CCR6) are closely related to angiogenesis, inflammation, immunity, tumor and diabetes development, and the potential components may exert anti-diabetic and COVID-19 effects by modulating these targets (Ito et al, 2011; Wu et al., 2019; Ma et al., 2019; Huang et al., 2020; Li et al., 2022)

3.5. Molecular docking validation

The affinities of compound **17** with AGTR1, VDR and PLG were found to be −9.7 kcal/mol, −8.2 kcal/mol and −8.1 kcal/-mol, respectively. In addition, compound **1** and AGTR1 protein with an affinity of −8.6 kcal/mol, compound **18** and CCR6 protein with affinity of −9.2 kcal/mol, compound **9** and protein IL2 with affinity of −8.3 kcal/mol, and compound **10** and PLG protein with affinity of −8.3 kcal/mol. The above results suggest that the core targets corresponding to the compounds for treating diabetes and COVID-19 have important value (Fig. 7).

4. Discussion

Diabetes and COVID-19 are both serious threats to human life and quality of life, and there is a linkage effect between them. Clinical studies have shown that some of COVID-19 inpatients without any prior medical history or diabetic problems had elevated blood glucose, suggesting that COVID-19 is associated with abnormal regulation of glucose metabolism (Francesco et al., 2020). Further, it was found that both normoglycemic and abnormal COVID-19 patients have insulin resistance and abnormal cytokine expression (Chandrashekhar Joshi and Pozzilli, 2022). COVID-19 virus has a direct impact on the pancreas, and the pancreas is a target of COVID-19 virus that not only causes acute symptoms during hospitalization, but may also affect the patient's long-term health (Tang et al., 2021; Wu et al., 2021). How to improve COVID-19-associated dysglycemia? How to find effective drugs for treating diabetes and COVID-19 in the same time? These are all hot issues of interest to researchers.

Modern studies have shown that Guizhou medicinal plants in China contain a large number of anti-diabetic, anti-inflammatory and anti-viral active compounds, which have

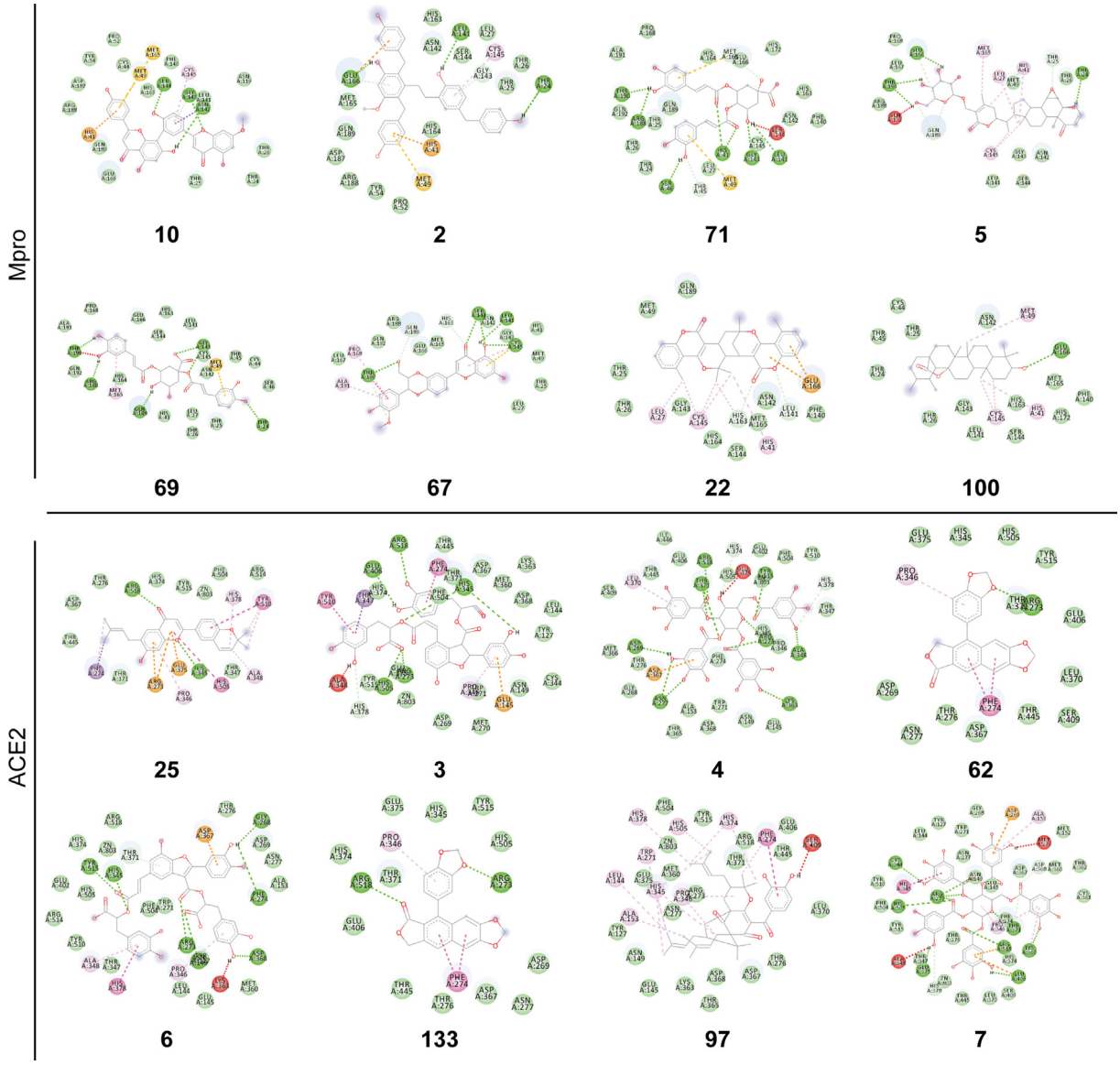


Fig. 3 The typical results of compounds for treating COVID-19.

good development and application values, like *Cyclocarya paliurus* (Batal.) Iljinsk. (Chen et al., 2018), *Musa basjoo* Sieb. et Zucc. (Wu et al., 2017), *Polygonum perfoliatum* L. (Zhang et al., 2010), *Bidens bipinnata* L. (Zhang et al., 2017), *Gynostemma pentaphyllum* (Thunb.) Makino (Bai et al., 2018). Therefore, it is suggested that the discovery of potentially active compounds from medicinal plants in Guizhou for treating diabetes and COVID-19 is a feasible and important way. Literature reports have found that Mpro and ACE2 are potential targets for discovering innovative drugs against COVID-19 (Hassam et al., 2022; Ong et al., 2022). In this work, more than 80 Miao medicines with "return to the lung channel" and "clear heat and detoxify" were sorted. With the improvement of modern isolation and analytical techniques, many compounds with novel structure have been reported in Miao medicine. Therefore, we took special care to collect the compounds of Miao medicines that are not included in the TCMSP database. In the search for potent drugs for COVID-19, raltegravir, ritonavir, lopinavir, and nirmatrelvir are all thought to improve the development of COVID-19 (Klement-Frutos et al., 2021; Akinosoglou et al., 2022; Zapata-Cardona et al., 2023) . The modern widely used clinical treatment for COVID-19 is the nirmatrelvir tablet/ritonavir tablet combination package, which has been used to stop the progression of novel coronavirus infections to severe disease with good results. Molecular docking results revealed good affinity of raltegravir, ritonavir, lopinavir, and nirmatrelvir with both Mpro and ACE2. It is very encouraging that a large number of active compounds against COVID-19 were screened using Mpro and ACE2 as target proteins using the molecular docking technique, which are of great value for the search of innovative drugs against COVID-19. Further, the active compounds constitute a special small molecular library of Miao medicines against COVID-19, and the components with better affinity are mainly flavonoids and phenylpropanoids. A large number of flavonoids and phenylpropanoids have been reported to

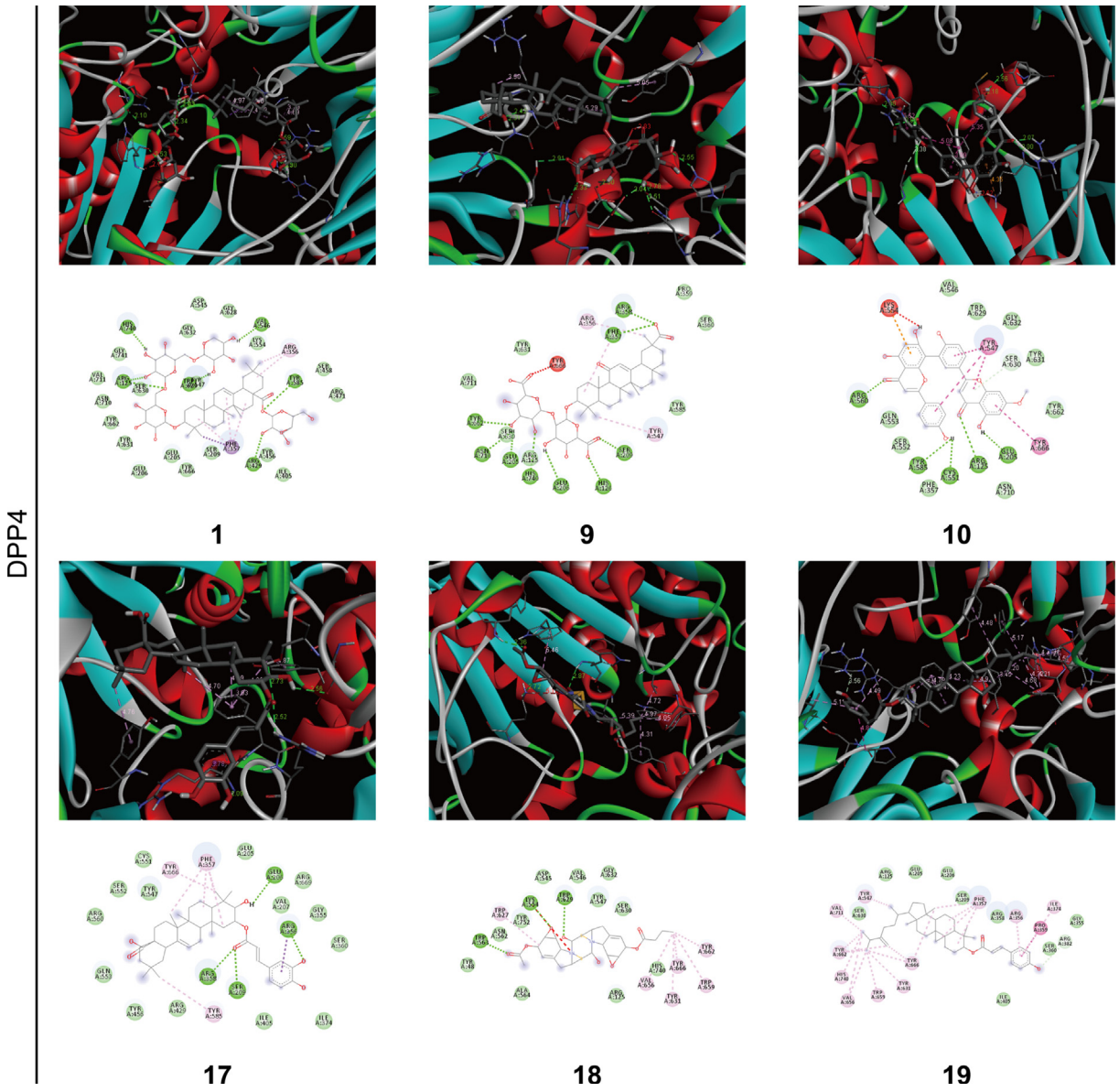
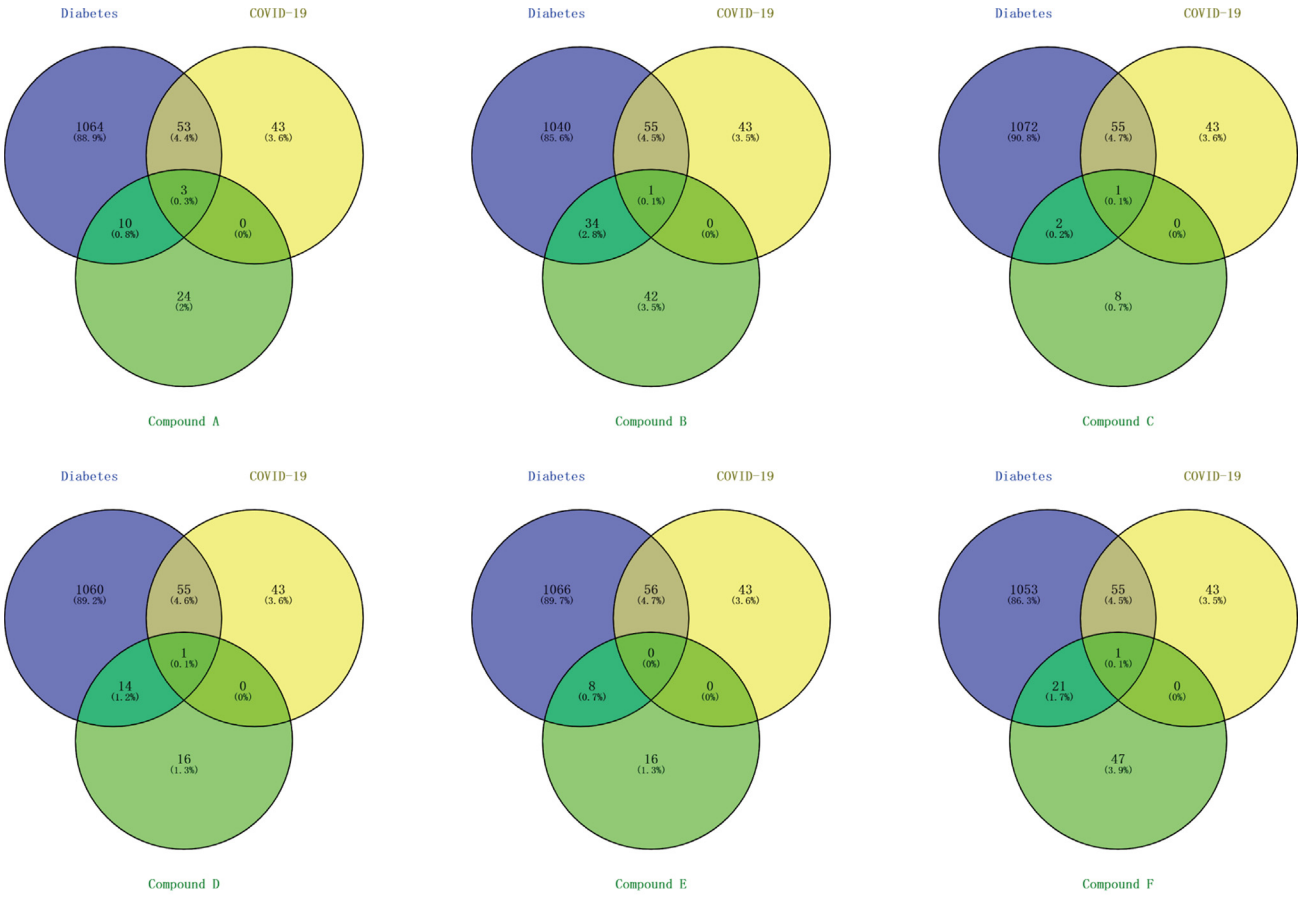


Fig. 4 The typical results of compounds for treating diabetes and COVID-19.

have good antiviral activity (Jo et al., 2020; Wahab et al., 2022).DPP4 plays an important role in inflammatory response and insulin regulation. In diabetes, DPP4 inhibitors are novel hypoglycemic agents with a unique mechanism of action to lower blood glucose by inhibiting DPP4 enzyme activity and are currently recommended for glycemic control in patients with type 2 diabetes (Rosenstock et al., 2019).The substrates of action of DPP4 enzymes include glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), and DPP4 inhibitors directly stimulate insulin regeneration and insulin secretion in pancreatic β-cells by protecting GLP-1 and GIP from excessive degradation and inactivation by DPP4 enzymes, directly stimulating insulin regeneration and insulin secretion from pancreatic β-cells, thereby lowering blood glucose (Hasan and Hocher, 2017; Hasan et al., 2019). For COVID-19, recent evidence suggests that DPP4, which is spread throughout the body, is a potential target for COVID-19 therapy and that the body's excessive inflammatory response to the virus may be mediated in part by DPP4 (Li et al., 2020). Therefore, DPP4 is an important common target for treating diabetes and COVID-19. Compared to the positive drugs (gemigliptin, sitagliptin and teneligliptin), potential compounds **1**, **9**, **10**, **17**, **18** and **19** for treating anti-diabetes and COVID-19 were identified. It has been reported that compound **17** has good antioxidant activity, compound **9** has antidiabetic activity, and compound **10** has potential for use against COVID-19 (Yang et al., 2007; Tan et al., 2022; Maione et al., 2019; Dey et al., 2022). These compounds have good potential for treating diabetes and COVID-19. Of course, *in vitro* and *in vivo* experiments are still needed to validate the results of this screening.

Novel compounds obtained from natural medicinal plants are characterized by multi-target and multi-pathway actions in the treatment of diseases, but how to deeply reveal their molecular mechanisms of action in the treatment of diseases is still an unsolved problem. In recent years, new methods



Compound A: 3-O-β-D-Xylopyranosyl-(1-6)-β-D-glucopyranosyl-(1-6)-β-D-glucopyranosyl oleanolic acid 28-O-β-D-glucopyranosyl ester
Compound B: Glycyrrhizic acid
Compound C: Sequoiaflavone
Compound D: 2-O-Caffeoyl maslinic acid
Compound E: Ambewelamide A
Compound F: Pholidotin

Fig. 5 The Venn diagrams among typical compounds, diabetes and COVID-19.

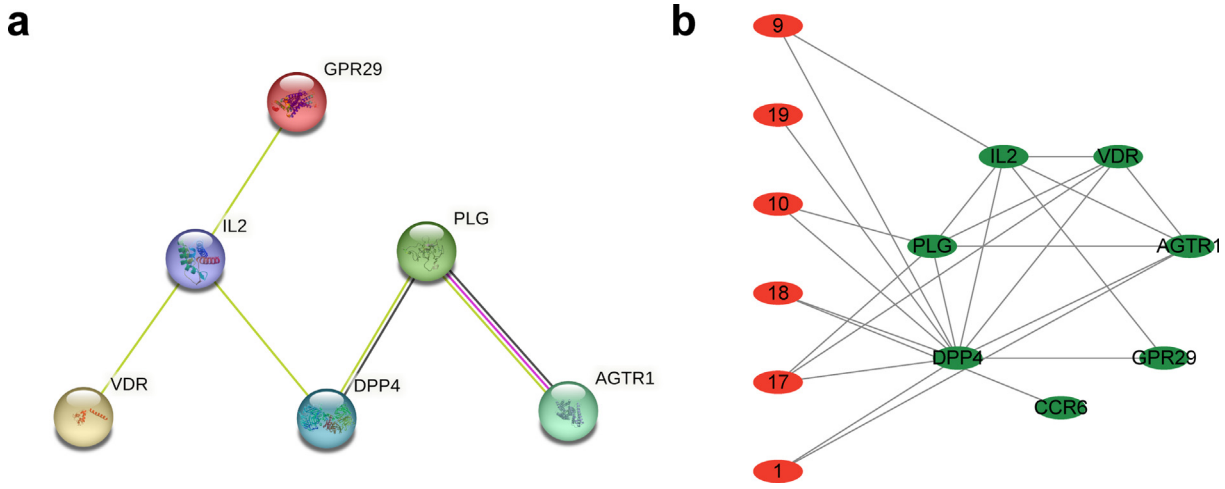


Fig. 6 The results of bioinformatics analysis.

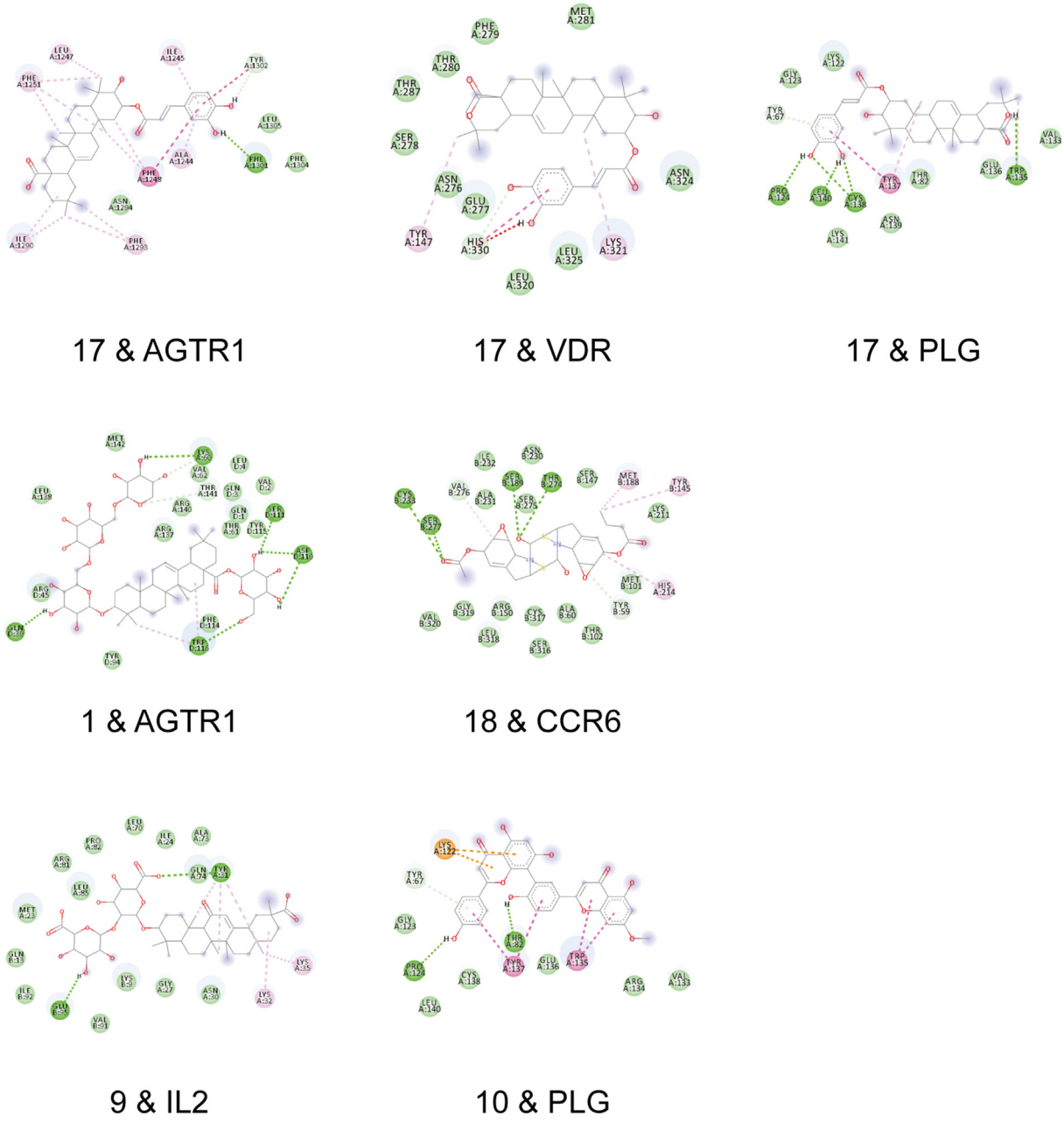


Fig. 7 The results of molecular docking validation.

and techniques have been used to study the underlying mechanism of drug action (Zhang et al., 2022). Bioinformatics can explore the mechanism of drug action from multiple levels, has been widely applied. Our work identified AGTR1, VDR, PLG, CCR6 and IL2 as the core targets of the potential compounds for treating diabetes and COVID-19 by bioinformatics analysis. The potential compounds may exert therapeutic effects through multiple pathways. According to reports, AGTR1 gene polymorphism may be associated with the development of type 2 diabetes, and this gene has hypomethylated DNA status in COVID-19 patients' raw data (Xie et al., 2008; Ahmadi Badi et al., 2022). AGTR1 is closed to PLG in the protein interaction network (Fig. 6a), and this target has potential as a common target for the treatment of diabetes and COVID-19 linkage. PLG activation is observed in diabetes mellitus, COVID-19 patients have CCR6 enrichment in their lungs, and IL-2 level was elevated in severe patients and decreased in critical patients with COVID-19 pneumonia (Geiger and Binder, 1991; Saris et al., 2021; Shi et al., 2020). These reports suggest that PLG, CCR6 and IL2 are all important targets for intervention in diabetes and COVID-19 linkage, indicating the reliability of the results of the bioinformatics analysis. In addition, the FokI polymorphism of the VDR gene has been found to be a risk factor for type 2 diabetes (Li et al., 2013), and new research provides evidence of an impaired vitamin D gene signature in $CD4^+$ T cells in patients with severe COVID-19 (Kolls and Garry, 2022). Potential components may exert anti-diabetic and anti-COVID-19 effects through VDR modulation of immune inflammation.

In summary, a large number of anti-COVID-19 compounds were screened from Miao medicine by molecular docking techniques. Further, the potential compounds **1**, **9**, **10**, **17**, **18** and **19** for anti-diabetes and anti-COVID-19 were obtained and they could act on multiple closely related targets simultaneously, which provides good options for the prevention and treatment of diabetes and COVID-19.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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