Investigation of Potential therapeutic value of Shuanghuanglian Chinese medicine based on network pharmacology for coronavirus pneumonia

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Research Article

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Abstract

Objective: The interaction network between coronavirus pneumonia and Shuanghuanglian was established to explore the potential therapeutic effect of the active ingredients of Shuanghuanglian on coronary virus pneumonia.

Methods: Using the TCMSP database, the effective components of Shuanghuanglian were obtained by screening consistent with oral utilization drug similarity and blood-brain barrier permeability thresholds, and the drug target prediction was performed. The SARS treatment target mining was performed through the GeneCards database, and the two data sets of therapeutic target and drug target were analyzed and the intersection was screened, and the wayne map was drawn. The intersection genes were used as potential therapeutic targets. Cytoscape 3.6 software was used to build a drug active ingredient-therapeutic target interaction network and analyze the active ingredient-therapeutic target point network Degree parameters to find important active ingredients and targets. Using DAVID and String databases to perform GO,KEGG enrichment analysis and protein interaction analysis on the intersection genes to find out the potential signal pathway of Shuanghuanglian against SARS.

Results: 43 effective components against SARS were screened, including coptisine, Mandenol, Ethyl linolenate, phytofluene, wogonin, FORSYTHINOL, baicalein, Moslossoflavone, Panicolin, etc. A total of 115 intersection genes with coronavirus pneumonia were screened as important treatment targets: based on the protein interaction network, Shuanghuanglian's therapeutic targets for diseases were significantly enriched in 1763 GO and 133 KEGG signaling pathways; The main action pathways are: responses to steroid hormones and ketones, and development of the reproductive system, responses to lipopolysaccharides, Toxins, responses to bacteria and aging, and effects on epithelial cell proliferation.

Conclusion: The active ingredients in Shuanghuanglian Chinese medicine compound can act on the disease-related target of coronavirus pneumonia and have potential therapeutic effects on coronavirus pneumonia.

Introduction

Viral pneumonia is a common respiratory disease, but it is still the leading cause of death in young children and the elderly in developing countries. The second leading cause of death was upper respiratory tract infection in 2013, according to The Global Burden of Diseas Study [1] reports, with an age-standardized mortality of 41.7 (95% CI 37.1-44.1). And the incidence of pneumonia caused by upper respiratory infection is about 1.5-14 per 1,000 people per year [2-4]. The incidence of community-acquired pneumonia is U-shaped. It is common in children under 5 years old and adults over 65 years old, and more common in men than in women. In 2008, 1.6 million children under 5 years old died of pneumonia [5]. Although Streptococcus pneumoniae is the main pathogen that causes community-acquired pneumonia worldwide [6, 7, 8] accounting for about 27.3%, but the virus is the most common cause of acute respiratory infections.
Unfortunately, so far no specific therapies for SARS-CoV, MERS-CoV and other HCoV infections have been found. Symptomatic treatment and supportive treatment are the main means for patients with HCoV infection. Although ribavirin and various types of interferon have become the most common treatment attempted by patients with SARS and MERS, the clinical effects are inconsistent when used alone to treat SARS. In vitro studies have shown that the combined use of IFN-β can make these two drugs have better antiviral activity, but the clinical efficacy is still controversial (16). At present, the 2019-nCoV new coronavirus epidemic outbreak in the world. From the current reports in various places, the structure, function, clinical symptoms and disease progression of the emerging coronavirus are extremely similar to SARS-CoV. The current treatment measures for 2019-nCoV pneumonia are mostly referred to the treatment of SARS, and 2019-nCoV and SARS-CoV have high Sequence homology. Therefore, we take SARS-CoV as the main research object, and it is of great significance to find effective and low-toxicity drugs to treat coronavirus pneumonia.

Shuanghuanglian is a traditional Chinese medicine compound, which has the functions of relieving wind and relieving phlegm, clearing heat and detoxifying, and is widely used in China for fever and cold. It is reported that Shuanghuanglian can inhibit the production of proinflammatory cytokines and chemokines and help fight inflammation and immunity. Regulating effect in the rat model of chronic Pseudomonas aeruginosa pneumonia. Shuanghuanglian can increase the lung resistance of rats to chronic Pseudomonas aeruginosa. Shuanghuanglian is also an effective drug for upper respiratory tract infection and acute tonsillitis (17–20). By analyzing the chemical components and the action genes involved in the compound Chinese herbal medicine Shuanghuanglian and integrate them with viral Pneumonia related genes to build a drug-gene-disease interaction network. Through the analysis of the interaction network, we predict whether Shuanghuanglian can act on coronavirus pneumonia and treat it.

1 Materials And Methods

1.1 Acquisition of Active Components and Target Genes of Shuanghuanglian

In this study, the traditional Chinese medicine system pharmacology analysis platform (http://tcmspw.com/tcmsp.php) was used to search for "Hydronic honeysuckle", "Scutellaria baicalensis", "Forsythia" three flavors of traditional Chinese medicine ingredients as Herb name, using oral bioavailability (OB). Drug-like properties (DL) and cell penetration rate assessment (caco-2) are used as screening indicators, and OB ≥ 30%, DL ≥ 0.18, and caco-2 ≥ 0.4 are selected as the active ingredients that meet the conditions. The activity of Shuanghuanglian was obtained through the TCMSP database. The target corresponding to the component is entered into the uniprot database (https://www.uniprot.org/) to obtain the standard gene name of the drug target.

1.2 Screening of target genes for severe acute respiratory syndrome (Severe Acute Respiratory Syndromes, SARS)
Search the Gene Cards (https://www.genecards.org) database for "Severe Acute Respiratory Syndromes" as a keyword to search for target genes related to severe acute respiratory syndrome.

1.3 Core target screening

Use Venny2.1 (http://bioinfogp.cnb.csic.es/tools/venny/index.html) online tool to draw a Wayne diagram of Shuanghuanglian related active ingredient target and Sars target to obtain its intersection target. Investigate the targeting effect of the active ingredients of Shuanghuanglian on Sars target.

1.4 Component-target network construction and topology analysis

The compound-target interaction network and the Shuanghuanglian pharmacological component-target interaction network were constructed by Cytoscape 3.6 software. Traditional Chinese medicine components or targets are represented as nodes in the network, and their relationship is represented as edges. Using Net-workAnalyzer computational node degree (Degree) parameters in Cytoscape3.6 software to evaluate the importance of medicinal ingredients and targets.

1.5 Construction of Shuanghuanglian target protein interaction (PPI) network

Enter the obtained intersection target genes into the String database (http://string-db.org), set the species to "Homo sapiens", select the data with a confidence level higher than 0.7, and obtain the protein interaction information corresponding to the intersection genes, and use the online tool to draw the protein mutual aid network diagram.

1.6 Enrichment analysis and pathway analysis

The obtained intersection genes were fed into the DAVID database (https://david.ncifcrf.gov/) for gene ontology (GO) biological process enrichment analysis and KEGG pathway enrichment analysis (p < 0.05). GO and KEGG are displayed in the form of bubble charts through R-studio software.

2 Results

2.1 Analysis of Shuanghuanglian Active Ingredients and Their Targets

Traditional Chinese Medicine System Pharmacology Database and Analysis Platform (TCMSP) (http://tcmspw.com/tcmsp.php) is a network pharmacology database that contains information on traditional Chinese medicine ingredients and their corresponding targets. This database contains the absorption of traditional Chinese medicine ingredients distribution, metabolism, and key parameters of excretion, including drug similarity (DL), oral bioavailability (OB), blood-brain barrier transmission rate (BBB), etc. This study uses the TCMSP analysis platform to identify "Honeysuckle", "Scutellaria baicalensis", Forsythia "three Chinese medicine ingredients were searched as Herb name, using oral bioavailability (OB), Drug-likeness (DL) and cell penetration rate assessment (caco-2) as screening indicators, select OB≥30%, DL≥ 0.18, caco-2≥0.4 as eligible active ingredients. The target corresponding to the active ingredient of Shuanghuanglian is obtained through the TCMSP database and
entered into the uniprot database (https://www.uniprot.org/) to obtain the standard gene name of drug target. 45 active molecules are now analyzed, including Mandenol, Ethyl linolenate, beta-carotene, ZINC03978781: 5-hydroxy-7-methoxy-2-(3,4,5-trimethoxyphenyl) chromone, beta-sitosterol, Stigmasterol, wogonin, (3R,4R)-3,4-bis[(3,4-dimethoxyphenyl)methyl]oxolan-2-one (+)-pinoresinol monomethyl ether, ACon1_001697: (+)-pinoresinol monomethyl ether-4-D-beta-glucoside, t3beta-Acetyl-20,25-epoxydammarane-24alpha-ol, Mairin, FORSYTHINOL, (-)-Phillygenin, hyperforin, Onjixanthone, beta-sitosterol, bicuculline, acacetin, wogonin, (2R)-7-hydroxy-5-methoxy-2-phenylchroman-4-one, baicalein, Dihydrobaicalin, q5, Salvigenin, 5',2',6'-Trihydroxy-7,8-dimethoxyflavone, Skullcap flavone II, oroxylin a, Panicolin, 5',7,4'-Trihydroxy-8-methoxyflavone, NEOBALICALEIN, DIHYDROOROXYLINC, beta-sitosterol, sitosterol, 5',2'-Dihydroxy-6,7,8-trimethoxyflavone, Stigmasterol, coptisine, bis[(2S)-2-ethylhexyl] benzene-1,2-dicarboxylate, Diopropiberberine, Moslosooavone, 11,13-Eicosadienoic acid, methyl ester, 5,7,4'-trihydroxy-6-methoxyflavone, rivularinin.

According to the chemical composition information of Shuanghuanglian, its target targets were predicted, and 122 standard gene names corresponding to molecular targets were obtained.

ACHE, ADH1C, ADRA1A, ADRA1B, ADRA2A, ADRA2D, ADRB1, ADRB2, AHR, AHSA1, AKR1B1, AKT1, ALB, ALDH3A1, ALOX12, APOD, AR, BAX, BBC3, BCL2, BMP2, CACNA2D1, CASP3, CASP7, CASP8, CASP9, CAV1, CCL2, CCNB1, CCND1, CDKN1A, CHEK1, CHRM1, CHRM2, CHRM3, CHRM4, CHRM5, CHRNA2, CRH, CTNNB1, CTRB1, CXCBL, CYCS, CYP1A2, CYP2C9, CYP3A4, EGLN1, EIF6, ESR1, ESR2, F3, F7, FASLG, FASN, FN1, FOS, FOSL1, FOSL2, GABBR1, GABRA1, GJA1, GJB1, GNRH1, GNRHR, GRM1, GRM5, GSK3B, HIF1A, HMOX1, ICAM1, IFI6, IL6, JUN, KCHN2, KDR, LTA4H, MAOA, MAOB, MAP2, MAPK14, MCL1, MMP1, MMP10, MMP2, MMP9, MPO, MYC, NCOA1, NCOA2, NFATC1, NOS2, NOX5, NR1I2, NR3C1, NR3C2, OPRM1, PDE10A, PGR, PKIA, PLAU, PON1, PPARG, PRKCA, PRKCD, PRSS1, PTGER3, PTGS1, PTGS2, PYGM, RELA, RXRA, RXRB, SCN5A, SLC6A2, SLC6A3, SLC6A4, TDRD7, TEP1, TNFSF15, TP63, VCP, VEGFA.

2.2 Screening of target genes for severe acute respiratory syndrome (Severe Acute Respiratory Syndromes, Sars)

The GeneCards (https://www.genecards.org) database was used to search for target genes related to severe acute respiratory syndrome using "Severe Acute Respiratory Syndromes" as keywords, and 7820 gene targets were obtained.

2.3 Core target screening

Using Venny2.1 (http://bioinfogp.cnb.csic.es/tools/venny/index.html) online tool to draw a Venn diagram of Shuanghuanglian related active ingredient target and Sars target to obtain the intersection target 115(Figure 1), including ACHE, ADH1C, ADRA1A, ADRA1B, ADRA2A, ADRB1, ADRB2, AHR, AHSA1, AKR1B1, AKT1, ALB, ALDH3A1, ALOX12, APOD, AR, BAX, BBC3, BCL2, BMP2, CACNA2D1, CACNA2D1, CASP8, CASP9, CAV1, CCL2, CCNB1, CCND1, CDKN1A, CHEK1, CHRM1, CHRM2, CHRM3, CHRM4, CHRM5, CHRNA2, CRH, CTNNB1, CTRB1, CXCBL, CYCS, CYP1A2, CYP2C9, CYP3A4, EGLN1, EIF6, ESR1, ESR2, F3, F7, FASLG, FASN, FN1, FOS, FOSL1, FOSL2, GABBR1, GABRA1, GJA1, GJB1, GNRH1, GNRHR, GRM1, GRM5, GSK3B, HIF1A.
2.4 Component-target network construction and topology analysis

Compound-target interaction network and Shuanghuanglian medicinal ingredient-target interaction network were constructed by Cytoscape 3.6 software (see Figure 2). Traditional Chinese medicine ingredients or targets are represented as nodes in the network, a total of 159 between them. The connections are represented as edges, a total of 599.

2.5 Construction of Shuanghuanglian target protein interaction (PPI) network

Enter the obtained intersection target genes into the String database (http://string-db.org), set the species to "Homo sapiens", select the data with a confidence level higher than 0.7, and obtain the protein interaction information corresponding to the intersection genes and 5 cluster interaction networks (Figure 3). Cluster 1 has 38 nodes, including PLAU, MCL1, MMP1, ESR1, CCL2, PGR, GJA1, IL6, CTNNB1, PPARG, CXCL8, FASLG, RELA, CYCS, CASP9, FOS, JUN, MMP9, CASP3, CASP8, ICAM1, ALB, FN1, HIF1A, AKT1, HMOX1, KDR, CCNB1, VEGFA, CCND1, CDKN1A, MMP2, AR, MPO, MAPK14, PTGS2, IGF2, MYC. A total of 561 interaction lines. Cluster 2 has 8 nodes, including CHRM3, GRM5, CHRM1, GRM1, ADRA1A, ADRA1D, GNRHR, PRKCA, a total of 23 interaction lines. Cluster 3 has 14 nodes, CHRM2, ACHE, CYP2C9, CYP1A2, SLC6A4, GABBR1, OPRM1, PON1, GNRH1, MAOA, MAOB, ADRA2A, ADRA1B, ADRB1, a total of 41 interaction lines. Cluster 4 has 6 nodes, CAV1, AHR, ESR2, NR3C1, NOS2, GSK3B, a total of 9 interaction lines. Cluster 5 has 3 Node, NR1I2, RXRA, RXRB, a total of 3 interaction lines.

2.6 Target gene enrichment analysis

Using the David database to perform gene ontology analysis (Go analysis) on the core targets of sars, a total of 1763 go enrichment analyses were identified, which involved 1,542 biological processes (BP), 72 cell compositions (CC), 149 molecular functions (MF). Sorted according to the size of the P-value, each selected 10 enriched Go values for visual display (Figure 4A). The top 10 of the biological process (BP), cell composition (CC), and molecular function (MF) in GO analysis were shown in Table 1. We noticed that some biological processes may be related to steroid hormones, ketones, lipids, polysaccharides, toxic substances, bacterial origin molecules and reproductive systems, aging and epithelial cell proliferation were related; Shuanghuanglian's resistance to Sars may be related to the membrane cell composition such as cell membranes and pre-synaptic membranes, which may be related to DNA transcription, nuclear receptor. steroid hormone receptors, G-protein-coupled amine receptors, or neurotransmitter receptor activity.

Analysis of target KEGG pathway in acute respiratory distress syndrome
DAVID database was used to perform KEGG signal pathway enrichment analysis on core targets in the acute respiratory distress syndrome network, and visualized after sorting by $P$ value and Gene ratio (Figure 4B). In the analysis of KEGG signal pathway, the $P$ value and Gene Ratio of the top 20 signal pathways are shown in Table 2. The related parameters in the drawn bubble chart are shown in Table 3. The results show that Shuanghuanglian resists respiratory distress syndrome which mainly involves AGE-RAGE, IL-17, p53, TNF, estrogen, thyroid hormone and other signal pathways, Kaposi’s sarcoma-associated herpes virus, human cytomegalovirus, measles virus, HIV, hepatitis B, hepatitis C and other virus, viral infections, small cell lung cancer, colorectal cancer and other cancer related pathways and neuroactive ligand-receptor interactions, Apoptosis, Endocrine resistance and other pathways.

Discussion

In the past decade or so, several previously undiscovered and confirmed viruses have appeared around the world, which cause respiratory diseases that are highly contagious and highly lethal. Especially new coronaviruses such as: SARS-CoV, H1N1-CoV, H5N1-CoV, MERS-CoV can cause tens of thousands of people worldwide infect, hundreds of people die, and because of its infectiousness, whenever pneumonia caused by this virus breaks out, in order to stop the infection sources and routes of transmission inevitably take various isolation measures, which often lead to people's panic and the abnormal functioning of society, causing inestimable losses. The histopathological changes of viral pneumonia vary, and may be related to viral infection and complications. Usually, interstitial pneumonia with lymphocytic infiltration can be seen in viral pneumonia [21]. And fatal cases of Sars and H5N1 were found to be characterized by alveolar damage, peeling of lung cells, edema and the formation of transparent membranes [22, 23].

Recently, a new virus 2019-nCoV was discovered in Wuhan, China. It belongs to the Coronaviridae family as well as the SARS virus and the MERS virus. At present, the new virus pneumonia caused by it is becoming increasingly infected and deadly for many people. Human coronavirus is considered to be an important pathogen causing infections in children, the elderly and immunocompromised patients, including upper and lower respiratory tract infections and acute respiratory distress syndrome [24]. Between 2002 and 2003, a global outbreak caused by SARS virus, which has infected 8089 people worldwide and killed 916 people in just a few months (25). Viral pneumonia caused by SARS virus, patients usually start acutely, have flu-like symptoms, dyspnea, and recurrent or persistent fever. The imaging characteristics of SARS are similar to those of other community-acquired pneumonias.

At first, chest X-rays are normal, and then quickly develop into nodular shadows. Large patchy shadows or large airspace consolidation shadows are mainly concentrated in the lower lung and involving surrounding lung tissues. MERS Coronavirus is a causative agent of the Middle East Respiratory Syndrome. During 2012–2014, there was an outbreak of MERS Coronavirus in Saudi Arabia, with a total mortality rate of 35% -44% (26). In March, 2015, a large-scale MERS coronavirus pandemic occurred in South Korea, with 186 patients diagnosed and 38 deaths. The clinical symptoms of patients with Middle East Respiratory Syndrome are similar to those involving fever, cough, dyspnea and pneumonia. Infection may rapidly develop into acute respiratory distress syndrome, multiple organ failure, and death. Compared with SARS, MERS progresses to respiratory failure and causes is faster and causes acute kidney damage (27). What is
more frightening is for new coronaviruses like SARS-CoV. MERS-CoV have so far lacked effective clinical antiviral drugs. These patients mainly received supportive treatment. Although during the SARS-MERS outbreak, ribavirin and inflammatory corticosteroids or IFNα with immunoglobulin. Thymosin in combination therapy (28–34), but these treatments have not been tested in clinical trials, their efficacy is difficult to assess and retrospective analysis has not draw an effective treatment combination. In addition, according to previous reports, it is unknown whether ribavirin has a greater benefit to the disease than it does to the body when it is used alone. However, IFN was proved to be effective against MERS-CoV (35–37) in vitro, and demonstrated in the MERS rhesus (38) model, the combined use of IFNα and ribovirus can alleviate disease, but it also brings such things as: fatigue, depression, anemia and other side effects. These greatly limit the use of IFNα as a first-line drug (39–41). Therefore, it is particularly important to find drugs that have inhibitory or therapeutic effects on such viral pneumonia and have fewer side effects. Since Professor Tu Youyou won the Nobel Prize in Physiology or Medicine for discovering the therapeutic effect of artemisinin on malaria in 2015, the effect of Chinese medicine on the disease has quickly attracted the attention of the medical community (42,43). In addition to artemisinin many traditional Chinese medicines have been shown to play an important role in the disease, for example: curcumin in turmeric has been shown to inhibit ovarian cancer, skin cancer, colorectal cancer, head and neck squamous cell carcinoma, and gastric cancer (44–48). Ginsenosides extracted from Fax Chen, Panax ginseng, and cinnamon (Cinnamomum cassia Presl) can inhibit cell proliferation, migration, angiogenesis, and anti-drug resistance (49–57) Plays anti-cancer effects in colorectal cancer, breast cancer, liver cancer and lung cancer (32–35). Emodin can be isolated from rhubarb palm, Polygonum cuspidatum, Polygonum multiflorum and Cassia seed, which has anti-inflammatory, anti-oxidant, prevent hepatic fat accumulation and DNA damage (58–64) has been shown to slow nasopharyngeal cancer, gallbladder cancer, lung cancer, liver cancer, colorectal cancer, oral cancer, ovarian cancer, bladder cancer, prostate cancer, breast cancer, gastric and pancreatic cancer (65–77).

Shuanghuanglian is a traditional Chinese medicine compound consisting of honeysuckle, scutellaria baicalensis and forsythia, which has been widely used in China for a long time. Shuanghuanglian injection can inhibit the inflammation associated with viral encephalitis, and it has been reported that Shuanghuanglian can play anti-inflammatory and antioxidant roles in alveolar macrophages of rats. Shuanghuanglian injection can prevent H5N1 virus infection by inhibiting viral replication and reducing lung injury and can effectively exert anti-HAdV virus effects by inhibiting virus penetration (78–79 ). We analyze the effective compounds in Shuanghuanglian traditional Chinese medicine compound, explore the proteins and corresponding genes that they act on, and compare the genes that act with SARS-related genes, and find that these two types of genes have 151 common gene action targets. Then we used Shuanghuanglian active ingredients and disease target genes to build a drug-disease-gene interaction network map. We use the intersection target genes as potential target genes for Shuanghuanglian treatment of coronavirus pneumonia. These target genes were enriched by gene function and action pathways, and the results were found: the main pathways of action are the response to steroid hormones and ketones, the development of the reproductive system, the response to lipopolysaccharides. Toxins, the response to bacteria and aging, and the effect on epithelial cell proliferation. Coronavirus often causes viral pneumonia, destroys normal alveolar tissue, proliferates fibroblasts and aggregates a large number of
extracellular matrices, resulting in pulmonary fibrosis, resulting in severe loss of lung function. Corticosteroids, anti-inflammatory and supportive treatments are currently for diseases caused by the kind of coronavirus like SARS-CoV, but it is well known that large doses and prolonged use of corticosteroids can cause obesity, immune system disorders, corticosteroid signs, electrolyte disorders, gastrointestinal ulcers, and severe necrosis of the femoral head. According to our research, the active ingredients of Shuanghuanglian traditional Chinese medicine compound have an effect on the proliferation of epithelial cells and bacteria and aging. It also has an effect on the response of steroid hormones, lipopolysaccharides and toxins, so the compound Chinese herbal medicine Shuanghuanglian may play an important role in the treatment of diseases caused by coronavirus. On the other hand, we found that the effective ingredients of Shuanghuanglian. The main pathways enriched for target genes are: cytomegalovirus infection, immunodeficiency virus infection, apoptosis, endocrine resistance, IL-17 signaling pathway, p53 signaling pathway, TNF signaling pathway. Viral infection, low immune function, and lung tissue, fibrosis is a feature of diseases caused by, for example, SARS-CoV.

Conclusion

The signal pathways enriched in this study are closely related to the diseases caused by coronavirus, and it suggests the feasibility of Shuanghuanglian traditional Chinese medicine compound for the treatment of diseases caused by coronavirus such as SARS. The active ingredients in Shuanghuanglian Chinese medicine compound can act on the disease-related target of coronavirus pneumonia and have potential therapeutic effects on coronavirus pneumonia.

Declarations

Ethical approval and Consent to participate:

This article does not contain any studies with animals or human performed by any of the authors. All methods are carried out in accordance with relevant guidelines and regulations.

Consent for publication: Not applicable.

Availability of supporting data:

All datas are available. Please contact us to access if it is needed.

Competing interests: There is no conflict of interests in this study: all authors declare that they have no conflict of interest.

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Authors' contributions

Jiasheng Xu and Kaili Liao analysed most of the data, and wrote the initial draft of the paper.

Guanyu Zhang and Yiran Li contributed to refining the ideas, carrying out additional analyses and finalizing this paper.

Weimin Zhou and Jiehua Qiu contributed the central idea.

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Tables

Table 1 Top 10 biological processes (BP), cell composition (CC), and molecular function (MF) in GO analysis
| ONTOLOGY | Description |
|----------|-------------|
| BP       | response to steroid hormone |
| BP       | response to ketone |
| BP       | reproductive structure development |
| BP       | reproductive system development |
| BP       | response to toxic substance |
| BP       | response to lipopolysaccharide |
| BP       | response to molecule of bacterial origin |
| BP       | aging |
| BP       | epithelial cell proliferation |
| BP       | regulation of epithelial cell proliferation |
| CC       | membrane raft |
| CC       | membrane microdomain |
| CC       | membrane region |
| CC       | caveola |
| CC       | plasma membrane raft |
| CC       | presynaptic membrane |
| CC       | integral component of presynaptic membrane |
| CC       | integral component of postsynaptic membrane |
| CC       | intrinsic component of postsynaptic membrane |
| CC       | intrinsic component of presynaptic membrane |
| MF       | nuclear receptor activity |
| MF       | transcription factor activity, direct ligand regulated sequence-specific DNA binding |
| MF       | steroid hormone receptor activity |
| MF       | G protein-coupled amine receptor activity |
| MF       | steroid binding |
| MF       | G protein-coupled neurotransmitter receptor activity |
| MF       | protein heterodimerization activity |
| MF       | heme binding |
| MF       | DNA-binding transcription activator activity, RNA polymerase II-specific |
| MF       | tetrapyrrole binding |

*Table 2* Parameters related to bar graphs of signal pathways enriched by drug target genes acting on diseases
| Description                                                                 | GeneRatio | p.adjust |
|-----------------------------------------------------------------------------|-----------|----------|
| AGE-RAGE signaling pathway in diabetic complications                        | 19/105    | 4.09E-15 |
| Kaposi sarcoma-associated herpesvirus infection                              | 22/105    | 1.71E-13 |
| Human cytomegalovirus infection                                              | 22/105    | 6.35E-12 |
| Hepatitis B                                                                  | 19/105    | 1.06E-11 |
| Small cell lung cancer                                                       | 15/105    | 2.74E-11 |
| Colorectal cancer                                                            | 14/105    | 1.46E-10 |
| Proteoglycans in cancer                                                      | 19/105    | 3.86E-10 |
| IL-17 signaling pathway                                                      | 14/105    | 3.86E-10 |
| Fluid shear stress and atherosclerosis                                        | 16/105    | 6.11E-10 |
| Estrogen signaling pathway                                                   | 15/105    | 5.06E-09 |
| Measles                                                                      | 15/105    | 5.06E-09 |
| p53 signaling pathway                                                        | 11/105    | 3.26E-08 |
| TNF signaling pathway                                                        | 13/105    | 3.26E-08 |
| Apoptosis                                                                    | 14/105    | 3.42E-08 |
| Thyroid hormone signaling pathway                                            | 13/105    | 6.02E-08 |
| Endocrine resistance                                                         | 12/105    | 6.24E-08 |
| Apoptosis - multiple species                                                 | 8/105     | 7.33E-08 |
| Hepatitis C                                                                  | 14/105    | 1.46E-07 |
| Neuroactive ligand-receptor interaction                                      | 20/105    | 1.46E-07 |
| Human immunodeficiency virus 1 infection                                     | 16/105    | 1.48E-07 |

**Table 3** Parameters related to bubble maps of signal pathways enriched by drug target genes acting on diseases
| Description                                             | COUNT/105 | GeneRatio | p.adjust   |
|---------------------------------------------------------|-----------|-----------|------------|
| Kaposi sarcoma-associated herpesvirus infection         | 22        | 0.21      | 1.71E-13   |
| Human cytomegalovirus infection                         | 22        | 0.21      | 6.35E-12   |
| Neuroactive ligand-receptor interaction                  | 20        | 0.19      | 1.46E-07   |
| AGE-RAGE signaling pathway in diabetic complications     | 19        | 0.18      | 4.09E-15   |
| Hepatitis B                                             | 19        | 0.18      | 1.06E-11   |
| Proteoglycans in cancer                                 | 19        | 0.18      | 3.86E-10   |
| Fluid shear stress and atherosclerosis                  | 16        | 0.15      | 6.11E-10   |
| Human immunodeficiency virus 1 infection                | 16        | 0.15      | 1.48E-07   |
| Small cell lung cancer                                  | 15        | 0.14      | 2.74E-11   |
| Estrogen signaling pathway                              | 15        | 0.14      | 5.06E-09   |
| Measles                                                 | 15        | 0.14      | 5.06E-09   |
| Colorectal cancer                                        | 14        | 0.13      | 1.46E-10   |
| IL-17 signaling pathway                                 | 14        | 0.13      | 3.86E-10   |
| Apoptosis                                               | 14        | 0.13      | 3.42E-08   |
| Hepatitis C                                             | 14        | 0.13      | 1.46E-07   |
| TNF signaling pathway                                   | 13        | 0.12      | 3.26E-08   |
| Thyroid hormone signaling pathway                       | 13        | 0.12      | 6.02E-08   |
| Endocrine resistance                                    | 12        | 0.11      | 6.24E-08   |
| p53 signaling pathway                                   | 11        | 0.10      | 3.26E-08   |
| Apoptosis - multiple species                            | 8         | 0.08      | 7.33E-08   |

**Figures**
Figure 1

venn diagram of Shuanghuanglian related active ingredient gene target and SARS disease gene target
Figure 2

Shuanghuanglian active ingredient-drug gene target-disease gene target interaction network
**Figure 3**

3A: protein interaction network for drug gene targets acting on diseases. 3B-F: 5 cluster interaction networks
Figure 4

4A: Gene enrichment analysis of drug gene targets acting on diseases 4B: Signal pathway analysis of drug gene targets acting on diseases