



# In Silico Prediction of Molecular Targets of Astragaloside IV for Alleviation of COVID-19 Hyperinflammation by Systems Network Pharmacology and Bioinformatic Gene Expression Analysis

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**Introduction:** The overproduction of cytokines and chemokines caused by excessive and uncontrolled inflammation contributes to the development of COVID-19. Astragaloside IV is considered as an anti-inflammatory and antioxidant agent. This study aimed at undertaking a network pharmacology approach and bioinformatics analysis to uncover the pharmacological mechanisms of Astragaloside IV on COVID-19.

**Methods:** Potential targets of Astragaloside IV were screened from public databases. Differentially expressed genes (DEGs) in SARS-CoV-2 were screened using bioinformatics analysis on the Gene Expression Omnibus (GEO) datasets GSE147507. Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were subsequently performed. The overlapping genes, GO terms and KEGG pathways between Astragaloside IV targets and SARS-CoV-2 DEGs were confirmed, and the location of overlapping targets in the key pathways was queried using KEGG Mapper.

**Results:** A total of 425 potential targets of Astragaloside IV were screened. Besides, a total of 546 DEGs were identified between SARS-CoV-2 infected samples and control samples, including 380 up-regulated and 166 down-regulated genes. There was a significant overlap in GO terms and KEGG pathways between Astragaloside IV targets and SARS-CoV-2 DEGs. The shared genes included MMP13, NLRP3, TRIM21, GBP1, ADORA2A, PTAFR, TNF, MLNR, IL1B, NFKBIA, ADRB2, and IL6.

**Conclusions:** This study is the first to propose Astragaloside IV as a new drug candidate for alleviating hyper-inflammation in COVID-19 patients. Besides, the key targets and pathways may reveal the main pharmacological mechanism of Astragaloside IV in the treatment of COVID-19.

**Keywords:** COVID-19, Astragaloside IV, hyperinflammation, network pharmacological, cytokine storms

## INTRODUCTION

COVID-19 has reached pandemic proportions around the world. Severe acute respiratory distress syndrome (ARDS) represents an important clinical feature of COVID-19, and a primary cause of death in COVID-19 patients (McGonagle et al., 2020; Ramanathan et al., 2020; Wu et al., 2020). In response to SARS-CoV-2 infection, immune cells and nonimmune cells release large amounts of proinflammatory cytokines, which lead to “cytokine storms”. Clinical studies have revealed that COVID-19 patients admitted to intensive care have increased expression of inflammatory cytokines (IL-6, IL-10, IL-2, and IFN- $\gamma$ ). Other studies confirm that a large number of patients with severe COVID-19 are likely to suffer a cytokine storm syndrome (Huang et al., 2020; Shen et al., 2020; Ye et al., 2020). ARDS and cytokine storms occur very often in patients with COVID-19 since excess production of pro-inflammatory cytokines results in ARDS aggravation (Howell and Davis, 2018). Therefore, there is a need to search for therapies to reduce hyper-inflammation and improve prognosis in severe COVID-19 patients.

Huangqi (Radix Astragali Mongolici) is a Well-Known Chinese Tonic. According to the Chinese Pharmacopeia, it is the dried root of the leguminous plants *Astragalus mongholicus*. It has been widely used in ischemic cardio-cerebrovascular disease, viral hepatitis, kidney disease, and skin diseases for the nourishment of Qi and blood (Li et al., 2017; Gong et al., 2018).

More than 40 active constituents of astragalus root have been identified, with Astragaloside IV (PubChem, CID13943297) being the major active compound.

The pharmacopeia of the People’s Republic of China has regarded Astragaloside IV as the quality standard for *Astragalus membranaceus* injection (Cao et al., 2019; Wang C. J. et al., 2020). Astragaloside IV has been widely used due to its anti-inflammatory effects associated with various molecular mechanisms (Ren et al., 2013; Li et al., 2017). Astragaloside IV has been reported to decrease *TNF- $\alpha$* , *IL-1 $\beta$*  release, and the expression of other inflammatory cytokines by inhibiting the phosphorylation of *I $\kappa$ B* and decrease nuclear translocation of *NF- $\kappa$ B* (Huang et al., 2017). Astragaloside IV also suppresses neutrophils adhesion-related molecules (Shen et al., 1998; Jin et al., 2010).

Currently, no studies have reported the use of Astragaloside IV in the treatment of COVID-19. In this study, the network pharmacology approach and bioinformatics analysis were used to investigate the possible mechanism of action underlying the effectiveness of Astragaloside IV in the treatment of COVID-19. The analysis workflow of network pharmacology is shown in **Figure 1**.

## MATERIALS AND METHODS

### Potential Astragaloside IV-Related Targets

The 2D molecular structure and PubChem CID of Astragaloside IV were obtained from PubChem (<https://pubchem.ncbi.nlm.nih.gov/>), which is the world’s largest database of free access to

chemical information (Wang et al., 2017). To predict the potential targets for Astragaloside IV with the AUC >0.7, SwissTargetPrediction (<http://www.swisstargetprediction.ch/>), (Daina et al., 2019), Comparative Toxicogenomics Database (CTD, <http://ctdbase.org/about/>), (Davis et al., 2019) and TargetNet (<http://targetnet.scbdd.com>) (Yao et al., 2016) were used. Generate Conformers was confirmed, maximum generated conformations are 300, select targets set of Pharmacophore Mapping was chosen as Druggable Pharmacophore Models, then Astragaloside IV related targets were predicted using PharmMapper (<http://www.lilab-ecust.cn/pharmmapper/>) (Wang et al., 2017). However, due to the nonstandard naming, the names of the targets were converted to official symbols using the UniProt Knowledgebase (UniProtKB, <http://www.uniprot.org/>) and species was restricted to “Homo sapiens”.

### SARS-CoV-2 Related Genes

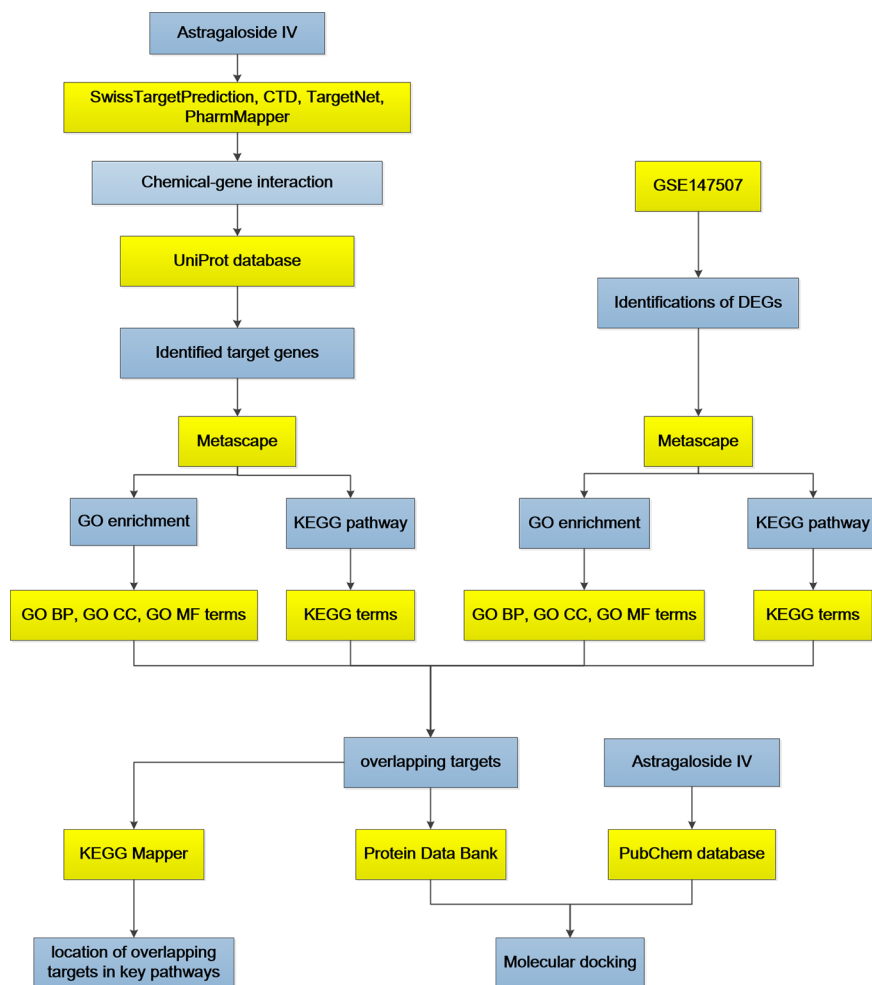
GSE147507 was downloaded from the GEO (<http://www.ncbi.nlm.nih.gov/geo/>) (Barrett et al., 2013) database. In the publisher’s study, the transcriptional responses of hosts to SARS-CoV-2 and other respiratory infections were systematically described. These data suggest that the unique transcriptional characteristics may be related to the pathogenesis of COVID-19 (Blanco-Melo et al., 2020). The transcriptional results of A549 cells (Series7) were selected for analysis. Impute and limma packages in R provided by the Bioconductor project (<http://www.bioconductor.org/packages/release/bioc/html/affy.html>) (Chen et al., 2007) were used to assess the transcriptional results. Quantile normalization and log<sub>2</sub>-transformation were performed before analyzing the matrix data. Original p-values were adjusted using the Benjamini-Hochberg method, and fold-changes (FC) were calculated using the false discovery rate (FDR). The  $|\log_2 FC| > 2$  and  $\text{adj.P.Val} < 0.05$  were used to filter the differentially expressed genes (DEGs).

### KEGG Pathway and GO Enrichment Analysis

A list of SARS-CoV-2 DEGs and Astragaloside IV related targets were submitted to Metascape (<http://metascape.org>) (Zhou et al., 2019), with the species limited to “Homo sapiens”. Functional enrichment analysis was performed based on the three categories of GO terms; Biological Processes, Cellular Components, and Molecular Functions. All genes present in the GSE147507 dataset were used as the enrichment background. Terms with a p-value < 0.01, a minimum count of 3, and an enrichment factor >1.5 were collected and grouped into clusters based on their membership similarities. The intersection of KEGG Pathways and GO terms were identified between Astragaloside IV-related targets and SARS-CoV-2 DEGs.

### PPI Network Construction and Key Pathways

SARS-CoV-2 DEGs utilized as hub proteins and submitted to String (<https://string-db.org/>) (Szklarczyk et al., 2019), with species limited to “Homo sapiens”. A confidence score >0.9 was used to obtain the PPI networks, which were visualized using Cytoscape 3.7.2 (<http://www.cytoscape.org/>)



**FIGURE 1** | The schematic diagram based on pharmacology analysis.

(Otasek et al., 2019). Overlapping targets were identified by considering the intersection of Astragaloside IV-related targets and SARS-CoV-2 DEGs. The location of overlapping targets in critical pathways was queried using KEGG Mapper.

### ***In Silico* Molecular Docking Study of Astragaloside IV Key Targets**

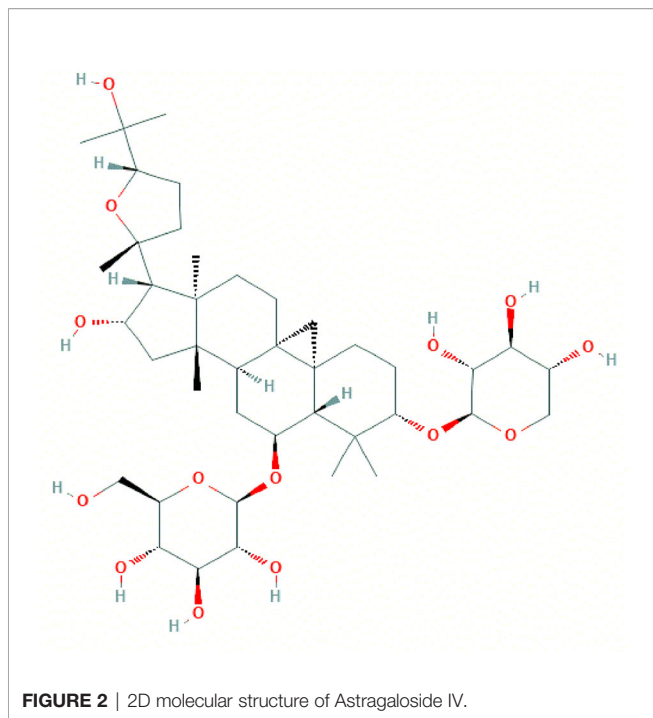
Autodock Vina was used to carrying out molecular docking of Astragaloside IV key targets (Trott and Olson, 2010). The PDB format molecular structure of Astragaloside IV was obtained from the PubChem database (<https://www.ncbi.nlm.nih.gov/>). The structures of the key targets were downloaded from the Protein Data Bank (<http://www.rcsb.org/>). The water molecules were deleted from the protein crystal structure, hydrogen atoms added, and charge calculated. The molecular docking mode of Astragaloside IV to the protein targets was selected as Local Search Parameters. The docking score was used to evaluate the theoretical binding affinities of Astragaloside IV to the key

targets. In order to compare the binding affinities of standard pharmacological immunosuppressive drugs with Astragaloside IV, the same methods were used to evaluate binding affinities of Rapamycin to the key targets.

## **RESULTS**

### **Potential Targets of Astragaloside IV**

The molecular structure of Astragaloside IV was download from PubChem (**Figure 2**), and PubChem CID of Astragaloside IV is 13943297. A total of five corresponding potential targets of Astragaloside IV were identified from TargetNet.19, while the corresponding potential targets of Astragaloside IV were identified from CTD. Besides, 154 corresponding potential targets of Astragaloside IV were identified using PharmMapper and 104 corresponding potential targets of Astragaloside IV were identified from SwissTargetPrediction. After data de-duplication,



282 potential targets were retained (**Figure 3, Supplemental file Table S1**).

### Identification of SARS-CoV-2 DEGs

A total of 23,710 genes and 546 DEGs were identified from SARS-CoV-2 infected samples compared with the control samples, including 380 up-regulated and 166 down-regulated genes. The identified DEGs between the control and SARS-CoV-2 groups were presented in volcano plots. **Figure 4** shows the heatmaps showing genes expression of the DEGs (**Supplemental file Table S2**).

### Gene Ontology and KEGG Enrichment Analysis of Astragaloside IV-Related Targets and SARS-CoV-2 DEGs

Based on GO enrichment, the SARS-CoV-2 DEGs were enriched in 150 terms, 127 in the category Biological Processes, and 23 in Molecular Functions. GO enrichment revealed that the DEGs were mainly involved in various biological processes (BP), including type I interferon signaling pathway, cellular response to type I interferon, response to type I interferon, defense response to a virus, mRNA binding involved in posttranscriptional gene silencing, response to a virus, defense response to other organism and negative regulation of viral genome replication. KEGG analysis revealed that the DEGs were enriched in nine pathways including, Influenza A, Measles, NOD-like receptor signaling pathway, Hepatitis C, Herpes simplex infection, Cytokine-cytokine receptor interaction, Chemokine signaling pathway. Top 20 terms in which the DEGs were enriched and ordered by *p*-value are listed in **Figure 5A**.

The Astragaloside IV related targets were enriched in 385 terms, including 341 in Biological Processes, 13 in Molecular Functions, and 31 in Cellular Components. The targets were involved in biological processes (BP) including, blood circulation, circulatory system process, G protein-coupled receptor signaling pathway, coupled to cyclic nucleotide second messenger, response to toxic substances, the vascular process in the circulatory system, regulation of system process, positive regulation of cell death, and regulation of tube diameter. KEGG analysis revealed that the targets were enriched in 74 pathways, all targets were primarily enriched in neuroactive ligand-receptor interaction, calcium signaling pathway, cAMP signaling pathway, pathways in cancer, and neurotrophin signaling pathway. The top 20 terms in which the targets were enriched and ordered by *p*-value are listed in **Figure 5B**.

The results revealed that there was a significant overlap in GO terms between Astragaloside IV targets and SARS-CoV-2 DEGs. The intersection of GO terms between Astragaloside IV related targets and SARS-CoV-2 DEGs included 34 terms (**Figure 7**). The top 10 overlapping GO terms ordered by *p*-value are listed in **Table 1**.

### PPI Network Analysis

Overlapping targets of Astragaloside IV and SARS-CoV-2 DEGs included MMP13, NLRP3, TRIM21, GBP1, ADORA2A, PTAFR, TNF, MLNR, IL1B, NFKBIA, ADRB, and IL6. PPI network can visualize and quantify the function of specific proteins in cells at the systematic level (Jordan et al., 2012). Therefore, a PPI network of overlapping targets and SARS-CoV-2 DEGs was constructed and the common targets marked (**Figure 6**). The location of overlapping genes and SARS-CoV-2 DEGs in the key pathways are listed in **Figure 7**.

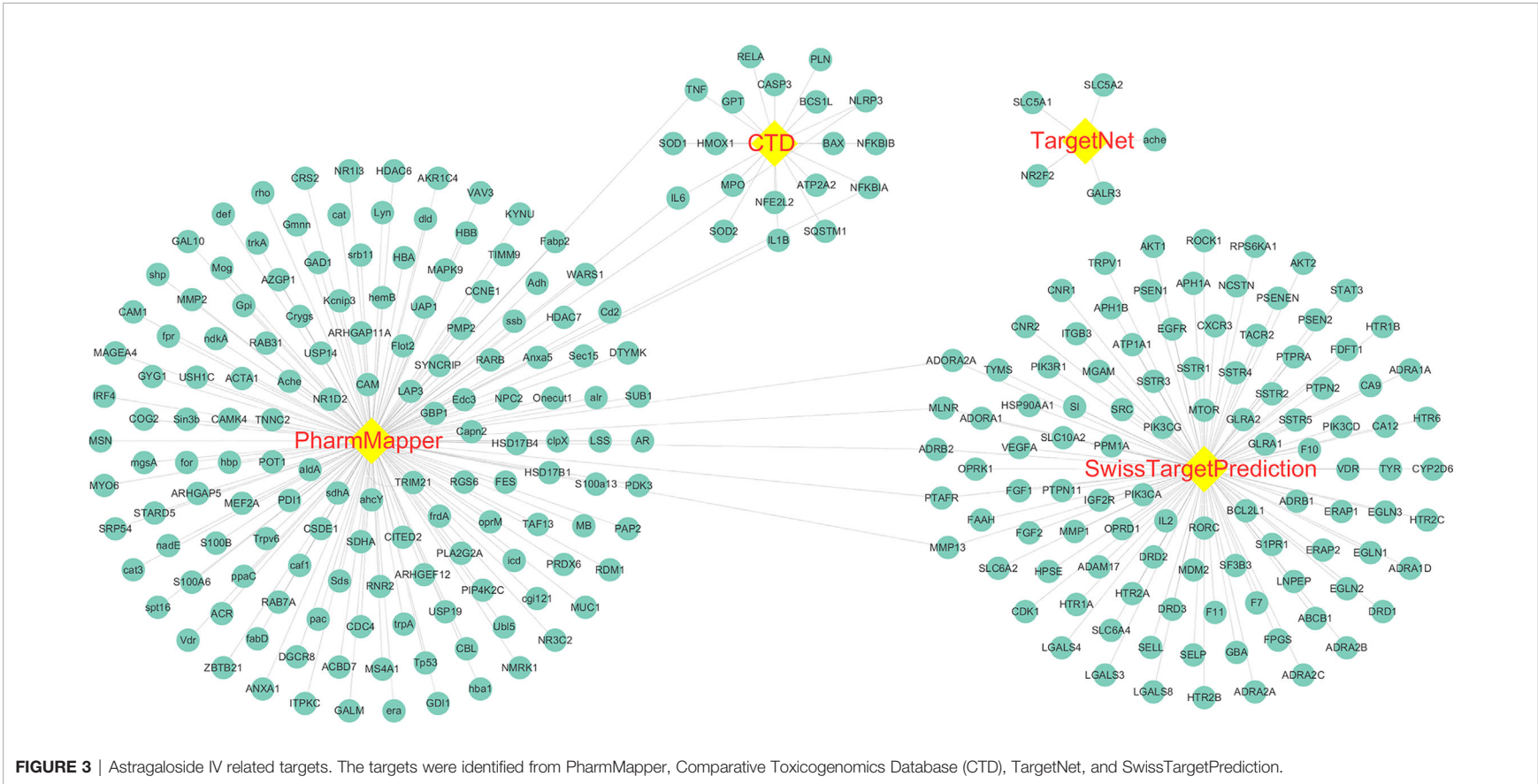
### Molecular Docking Analysis

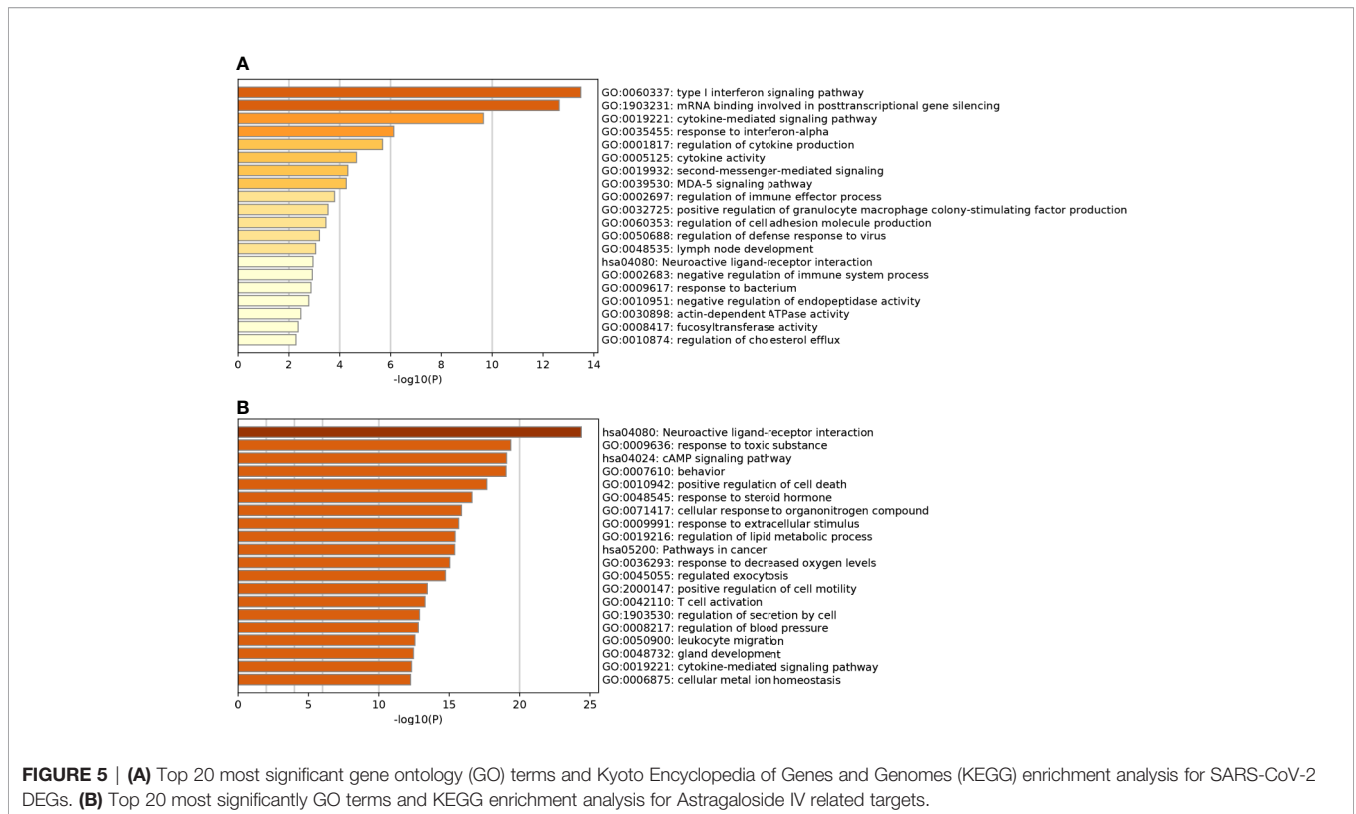
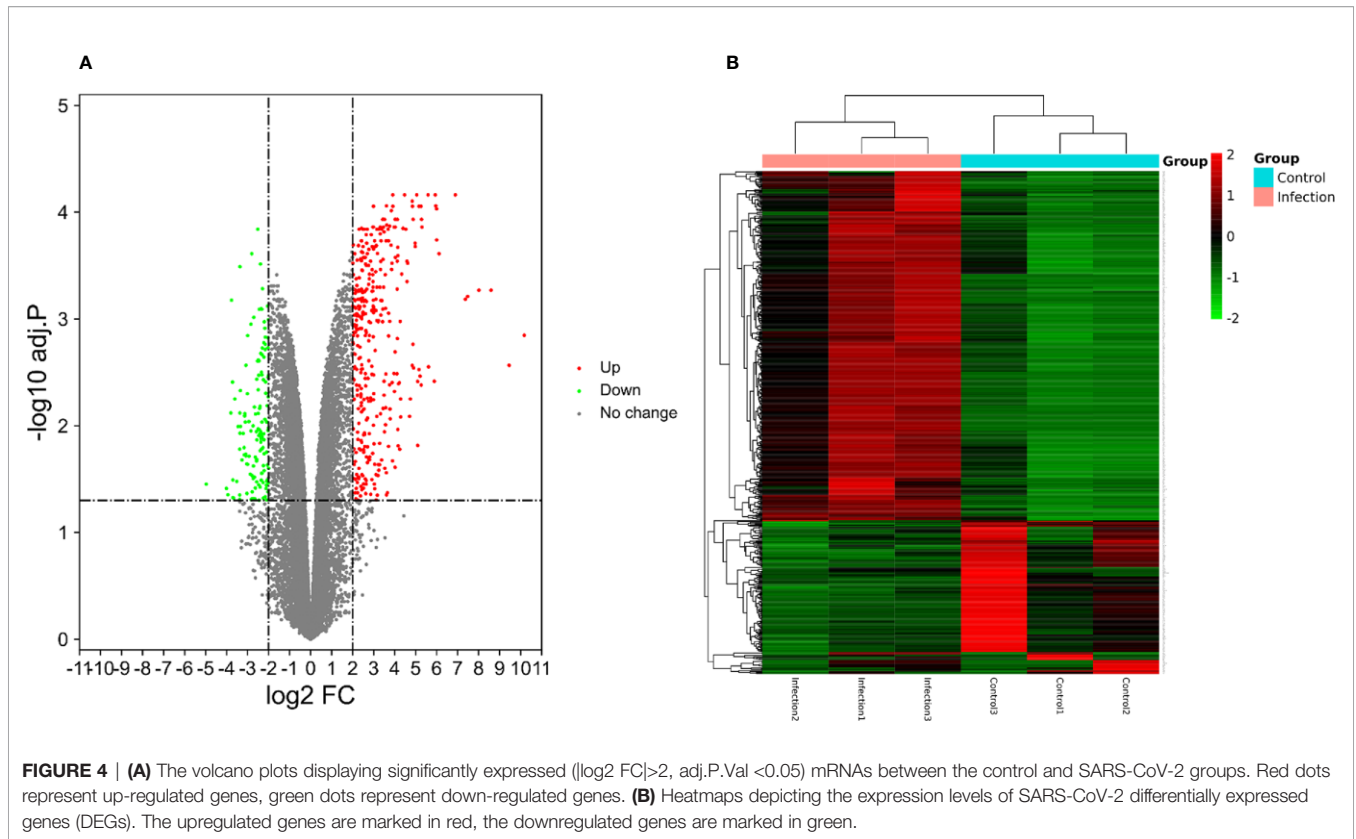
Molecular docking analysis was conducted to evaluate the binding affinity of Astragaloside IV with key target receptors. The results showed that docking scores of Astragaloside IV with MMP13, NLRP3, GBP1, ADORA2A, PTAFR, TNF, MLNR, IL1B, NFKBIA, ADRB2, and IL6 ranged from  $-6.72$  to  $-9.05$ . Particularly, Astragaloside IV presented the highest docking score with MMP13 and IL6 (docking score:  $-9.05$ ,  $-9.04$ ), demonstrating that Astragaloside IV is perfectly located inside the binding site together with MMP13 and IL6. Other key targets also showed an affinity with Astragaloside IV. Compared to Rapamycin, Astragaloside IV showed weaker binding affinities to these targets (**Figure 8; Table 2**).

## DISCUSSION

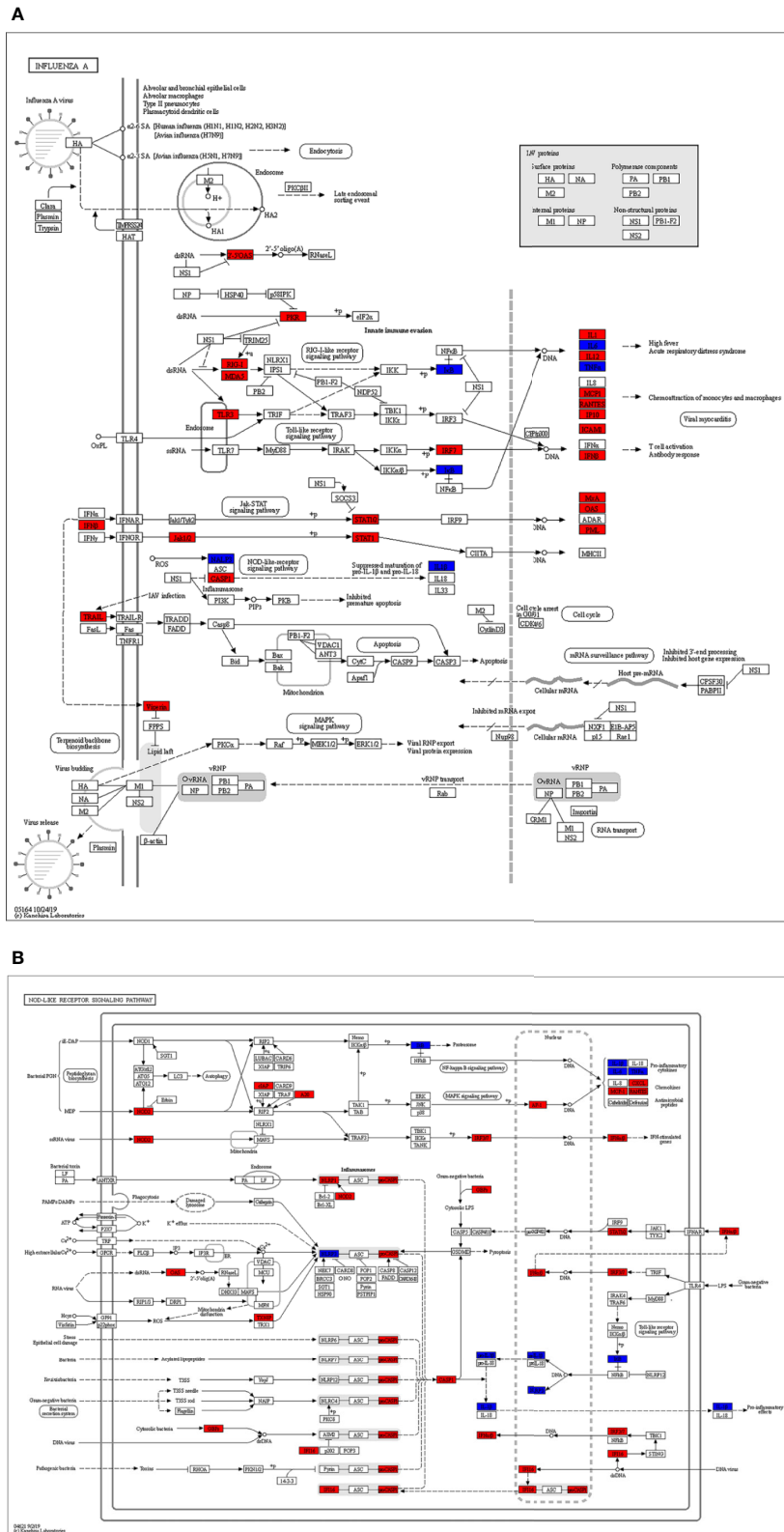
Astragaloside IV has been widely used in clinical practice (Qi et al., 2006; Xie et al., 2012; Yang et al., 2012). Pharmacokinetic properties of Astragaloside IV have been based on linear pharmacokinetics on doses ranging from 0.3mg/kg to 0.75mg/kg of Astragaloside injection. Astragaloside IV is safe and well-tolerated after intravenous infusion in clinical practice (Xu et al., 2013).











**FIGURE 7 |** The identified key pathways. **(A)** Influenza A pathway. **(B)** NOD-like receptor signaling pathway. The red marked nodes represent up-regulated SARS-CoV-2 differentially expressed genes (DEGs), while the blue marked nodes represent overlapping targets of Astragaloside IV and SARS-CoV-2.





## DATA AVAILABILITY STATEMENT

All datasets presented in this study are included in the article/**Supplementary Material**.

## AUTHOR CONTRIBUTIONS

CG and YH contributed equally to this study. CG and YH participated in the design of this study and performed

the statistical analysis. CG drafted the manuscript. All authors contributed to the article and approved the submitted version.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fphar.2020.556984/full#supplementary-material>

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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