To Explore the Mechanism of Tibetan Medicine Gaoyuan' an Capsule Improving Plateau Hypoxia Tolerance

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Research

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Abstract

Background: Tibetan medicine Gaoyuan 'an capsule (GYAC) is widely used to prevent pulmonary edema at high altitude, but the specific mechanism of its action has not been explored. Therefore, based on bioinformatics and network pharmacology, this study analyzed the mechanism of improving hypoxia tolerance of GYAC, and provided new ideas for the prevention of altitude disease.

Methods: The effective components and corresponding targets of *GYAC* were screened by using the Chinese herbal medicine network database, and the key targets of diseases were retrieved by using Genecards, OMIM and PubMed database with the key word "hypoxia". The drug targets and disease targets were mapped into common targets to obtain the final target. Cytoscape 3.7.2 was used to analyze the topological network and construct the Herbs-Components-Targets network and Core Targets-Signal Pathways network. GO function and KEGG enrichment analysis were performed to predict the mechanism of action, and molecular docking techniques were used to verify the binding force of target compounds and targets.

Results: The results showed that GYAC enhanced hypoxia tolerance by simultaneously regulating the functions of various signaling proteins, including *IL6*、*TNF*、*NOS3*、*VEGFA* etc. The main regulatory pathways were *HIF-1* signaling pathway, Chagas disease, and pathway in cancer. The main biological processes involved are the positive regulation of *RNA* polymerase II promoter transcription, the extracellular space as the cell component, and the cytokine activity as the molecular function. Molecular docking shows that hydrogen bonding is the main form of binding between drug molecules and proteins.

Conclusions: GYAC is mainly directed at the interaction of *HIF-1* signaling pathway with targets such as *IL6* and *TNF* to improve the body's hypoxia tolerance, that is, they are multi-pathway, multi-pathway and multi-target interaction.

1. Introduction

Continuous hypoxia at low pressure is a major feature of high-altitude environments, and the metabolic functions of skeletal muscle and heart are strongly influenced by the duration of exposure [1]. Many diseases arise from hypoxic environments, such as acute alpine disease, plateau brain edema, and plateau lung edema [2]. With the development of the world, more and more people enter the plateau region for tourism and work, which is extremely important to prevent the occurrence of altitude sickness.

GYAC is a commonly used medicine to prevent high altitude reaction, which is mainly composed of Astragalus membranaceus, Rhodiola, Panax quinquefolium and Salvia miltiorrhiza. Its main function is to improve hypoxia tolerance and enhance immunity, but the specific mechanism of improving hypoxia tolerance is not clear.

Astragaloside IV (*AST-IV*) isolated from Astragalus membranaceus has strong anti-inflammatory, anti fibrosis, anti oxidative stress, anti asthma, anti diabetes and immunomodulatory effects [3, 4]. It has been

proved that *AST-IV* can inhibit hypoxia induced apoptosis of *PC-12* cells by down regulating *miR-124* [5]. Hypoxia inducible Factor-1α (*HIF-1α*), a transcription complex, has become a key regulator of molecular hypoxia response, and is also a major regulator of homeostasis in hypoxic cells and systems by activating transcription of many genes [6], In addition, *AST-IV* upregulated *HIF-1* [7]. Rhodiola rosea is a common medicinal plant in Asian countries. It is reported that rhodiola rosea has significant anti-hypoxia, neuroprotective, anti-fatigue and radiation protective activities. It has protective activities against hypoxia both in vitro and in vivo [8, 9]. Rhodiola rosea alleviates apoptosis and mitochondrial energy metabolism disorders after hypoxia induced brain injury in rats by regulating *HIF-1 / microRNA 210 / ISCU1/2* (*COX10*) signaling pathway [10]. Saponins, the main bioactive component of Panax quinquefolium, have many pharmacological effects, such as regulating blood glucose, lowering blood lipid, anti-tumor, anti-oxidation, anti arrhythmia and improving myocardial ischemia. Danhong injection (*DHI*) is a traditional Chinese medicine extracted from Salvia miltiorrhiza and safflower. It protects myocardial cells from hypoxia / reoxygenation and *H2O2* induced injury by inhibiting the opening of mitochondrial permeability transition pore [11].

Traditional Chinese medicine (CM) is often used as a prescription for the treatment of diseases, but there is a lack of effective methods to study its complex chemical compounds, so the specific mechanism of action of CM is difficult to clarify [12]. The combination of network biology and multi-pharmacology is expected to expand the current opportunity space for drug-actionable targets and lay the foundation for an effective approach to drug discovery: network pharmacology [13]. Molecular docking is a theoretical simulation method to predict the binding mode and affinity of a drug by using the characteristics of the receptor and the way of interaction between the receptor and the drug molecule. It can reduce the time and consumables we experience in drug development, and at the same time, it has a strong practicality in structure-based drug design, lead optimization, biochemical pathway and drug design, which are the most attractive tools [14].

In this study, we used the network Pharmacology Method to predict the potential mechanism of GYAC in improving hypoxia tolerance. Our results may help to clarify how GYAC can effectively increase hypoxia and promote new milestones in the prevention of altitude sickness and altitude sickness. The flow chart of this research is shown in Fig. 1.

2. Materials And Methods

2.1 Compound screening and potential target prediction in GYAC

In order to collect the chemical constituents of four herbs in GYAC, we used the pharmacology database of traditional Chinese medicine system (TCMSP：*http://lsp.nwu.edu.cn/TCMSP.php*) [15], The drug screening threshold was set as OB (oral bioavailability) ≥ 30%, DL (similarity of patent medicine) ≥ 0.18, and the effective compound information and corresponding target of gaoyuan'an capsule were obtained. In addition, the comprehensive database of traditional Chinese medicine integrative database (TCMID：

http://183.129.215.33/TCMID/search/[16], PubMed and CNKI searched the TCMSP database for the compounds of traditional Chinese medicine which were not included in TCMSP.

2.2 Target gene prediction associated with hypoxia tolerance

Target genes related to hypoxia were obtained from genecards, OMIM and PubMed with the key word "hypoxia". The common target genes related to hypoxia of GYAC were obtained by mapping the targets of active ingredients and hypoxia related targets. Taking "Homo sapiens" as the research species, the predicted targets were selected and standardized by UniProt database.

2.3 Construction of network graph of target gene

Based on the above data set, the common target genes were introduced into string (*https://string-db.org/cgi/input.pl*) to establish PPI network interaction [17]. Cytoscape 3.7.2 (*http://www.cytoscape.org/*) [18] is an open source software platform that can be used to visualize complex networks and integrate different types of attribute data , Cytoscape 3.7.2 used to build and visualize PPI network [18], In order to reflect the complex relationship between active compounds and their potential targets, a " Herbs-Components-Targets " network diagram was established by using Cytoscape 3.7.2 [19]. In the network, the nodes represent the screened active components and targets, while the connections between nodes represent the interactions between these biological analyses. According to the degree value, the largest compounds were selected as ligands for molecular docking. The degree of a molecule represents the number of connections between the molecule and the target in the core architecture of the network [20], the higher the value, the more likely it will become the key component of GYAC.

2.4 Enrichment analysis of go function and KEGG pathway

The functional enrichment of Gene Ontology (GO) was analyzed by DAVID and the pathway enrichment analysis based on Kyoto Encyclopedia of genes and genomes (KEGG) was used to predict its mechanism. EHBIO (*https://www.ehbio.com*) it is used to process data and visualize the enrichment results of GO enrichment analysis and KEGG pathway analysis, including Biological Process (BP), Molecular Function (MF) and Cell Composition (CC).

2.5 Analysis of the core molecules of receptor

Through RSCB PDB database (*http://www.rcsb.org/*) from the interaction network of GYAC to improve hypoxia tolerance, the top two core protein receptors with the order of degree from high to low were selected, select the corresponding target protein structure and download its 3D structure pdb format file.

In PubChem database (*https://pubchem.ncbi.nlm.nih.gov/*) the SDF format file of 2D structure of core active compound was obtained, and its chemical structure was found by *UniProt* database (*https://www.uniprot.org/*). PyMOL software was used to remove water and original ligands from the original pdb file. Autodock charging software was used to add polar hydrogen to target protein receptor molecules. Molecular docking was realized through Autodock Vina and Python scripts. The lower the binding energy is, the better the affinity between receptor and ligand is. In this study, the binding energy ≤ - 5.0 kj/mol was selected as the screening basis for effective binding of compounds to target.

3. Results

3.1 Construction of Herbs-Compounds-Targets Network and PPI network analysis

A total of 98 active compounds were retrieved in the database, and 235 corresponding target proteins were removed, among which astragalus membranaceus and Rhodiola rosea had two identical compounds at the same time. 2998 hypoxia-related targets, 750 OMIM targets and 217 duplicates were removed from PubMed database after retrieving GeneCards database. First, the intersection of target proteins of active pharmaceutical ingredients, *GeneCards database, OMIM* database and PubMed database was used to obtain the common target of 28 gene targets of drugs and diseases. Meanwhile, the Wain diagram was obtained by using EHBIO online mapping tool platform, as shown in Fig. 2A. Secondly, in order to further explore the mechanism of action of GYAC and targets in hypoxia at protein level, 28 common targets were imported into string database for PPI network analysis, and the analysis results were imported into Cytoscape 3.7.2 to draw PPI network, as shown in Fig. 2B. In PPI network diagram, there are 28 nodes, 227 edges, and the average node degree is 16.2. In PPI network diagram, the larger the node and the darker the color, the greater the degree value. The larger the degree values are *IL6*, *TNF*, *NOS3*, *CCL2*, vegaf, etc., which indicates that these proteins have strong interaction ability with other proteins in the network and play an important role in PPI network, see Table 1 for the dimension of body. Third, 60 of the 28 common targets were corresponding to drug active components, and the Drug-component-target relationship was obtained. Cytoscape 3.7.2 was used to obtain the “Herb-compound-target” network diagram, there are 92 nodes and 245 edges, as shown in Fig. 3. Network topology analysis is carried out by using the NetworkAnalyzer function in Cytoscape 3.7.2. Degree of nodes is an important indicator to describe network nodes. From the perspective of compound analysis, according to the number of targets corresponding to the active components, the top 6 components were selected to obtain Table 2, among which Quercetin (MOL000098) and Luteolin (MOL000006) were the most important, both of which were found in astragalus and Rhodiola rosea. Therefore, the interaction between multiple components and multiple targets exists in GYAC, which further proves that GYAC has the synergistic effect of multiple components and multiple targets on improving hypoxia tolerance.

3.2 Enrichment analysis of GO function and KEGG pathway

In order to further understand the mechanism of action of the common target, GO enrichment analysis was performed, screening *P < 0.05*, take the top ten according to the size of *P* value, as shown in Fig. 4C. The results are as follows : (1) Biological Processes (BP) *206*, It mainly includes positive regulation of transcription from RNA polymerase II promoter, response to hypoxia, and positive regulation of gene expression, etc. (2) Cell Components (CC) *14*, mainly including extracellular space, cell surface and extracellular region, etc. (3) Molecular Function (MF) *32*, mainly including cytokine activity, enzyme binding and protein binding, etc. In addition, the main roles related to hypoxia were enriched by KEGG pathway, and 48 (*P < 0.05*) Signal pathway, it mainly involves *HIF-1* signaling pathway, Chagas disease (American trypanosomias) and infectious bowel disease (IBD), etc., as shown in Fig. 4B. At the same time, according to KEGG enrichment analysis results, we selected the first 17 pathways according to the corresponding target number of each pathway to obtain the " Target-pathway network" Fig. 5.

3.3 Molecular docking results

It is generally believed that the lower the binding energy between ligand and receptor, the more stable the binding conformation is, it is indicated that the ligand has certain binding activity, ≤ − 5.0 kcal/mol indicates that it has better binding activity, and ≤ − 7.0 kcal/mol indicates that both of them have strong binding activity. Firstly, through PPI network analysis, we found that *IL6* and *TNF* were closely related to the occurrence of hypoxia, through the “Herb-compound-target” network diagram, it was found that Quercetin (MOL000098) interacts with 20 targets and can interact with these two targets. Therefore, AutoDock Vina was further used in this study for molecular docking verification, and the results showed that quercetin and *IL6* had a binding capacity of -7.04 kcal/mol, and quercetin and *TNF* were − 8.0 kcal/mol. Finally, Pymol software was used for visualization processing of Quercetin with *IL6* and *TNF*, and the results showed that quercetin and *IL6* were mainly bound by 6 hydrogen bonds, with the main binding residues including *GLU-165*, *Pro-156*, *PRO41* and *THR-164*, etc. Quercetin and *TNF* were mainly bound by 4 hydrogen bonds, and the main binding residues were *ASN-112*, *GLU-110*, *GLU-102* and *ARG-103*, as shown in Fig. 6.

4. Discussion

Network pharmacology can provide a full or partial understanding of network theory and systems biology, making it a cutting-edge approach in drug discovery [21]It can also predict the interactions between multiple drugs - targets - diseases, so this study used its method to predict the mechanism of GYAC to improve hypoxia tolerance. Hypoxia is the fundamental result of high altitude exposure and severe disease. In high altitude areas, the partial pressure of oxygen decreases, leading to a decrease in the utilization rate of oxygen in the atmosphereb[22], this may lead to various pathophysiological symptoms, such as ischemia, high altitude reaction (including acute mountain sickness), high altitude pulmonary edema and high altitude brain edema [23], mental disorders and memory loss, insomnia, dizziness, nausea, irritation, dyskinesia [24, 25], pulmonary diseases [26], hypoxia can also cause biochemical changes of blood-brain barrier and left ventricular dysfunction [27, 28]. Hypoxia-inducible factor (*HIFs*) is the main regulator of angiogenesis during hypoxia [29]. In this study, The “Herb-compound-target”

network diagram shows that Quercetin, Kaempferol, Luteolin et al play an important role in the network, indicating their potential research value in therapy. At the same time, the active ingredient quercetin with the most active target protein was used for molecular docking verification, so as to verify our prediction results. The results of molecular docking showed that the interaction between hydrogen bonds and residues was the main form between active components and proteins. Research has shown that, quercetin can regulate the release of *IL-6*, *IL-8*, *TNF*, histamine and tryptase from mast cells [30]. Luteolin can reduce the expression of *VEGF* and promote angiogenesis [31], and antioxidant function [32]. Kaempferol can inhibit inflammation and oxidative stress [33].

In order to explore the mechanism of GYAC in improving hypoxia tolerance, we analyzed the candidate targets by performing go enrichment results, the main BP in our study include positive regulation of transcription from *RNA* polymerase II promoter,the main CC include extracellular space, cell surface and extracellular region, the main MF include cytokine activity, enzyme binding and identity protein binding, the main target proteins involved are *IL6*, *TNF*, *STAT3*, *VEGFA* and so on. *TNF - α* is a major regulator, which can induce the production of *IL- 1β*, *IL-6* and other cytokines, and participate in the process of oxidative stress and inflammatory injury [34].

In addition, the enrichment of KEGG pathway plays an important role in hypoxia, including *HIF-1* signaling pathway, Chagas disease (American trypanosomias) and inflammatory bowel disease (IBD). The concept that hypoxia can induce inflammation has been widely recognized in the study of hypoxia signaling pathway [35], *HIF-1* signaling pathway activates the expression of *VEGFA* in inflammatory response to counteract hypoxia and prevent renal tissue damage [36]. On the other hand, from our target pathway diagram, it can be clearly seen that *HIF-1* signaling pathway interacts with multiple targets, such as *IL6*, *NOS3*, *STAT3*, *VEGFA*, etc. not only that, it does not only act on one pathway, but also acts on multiple pathways, that is, multiple pathways and multiple targets regulate each other.

5. Conclusion

In general, we predicted that GYAC mainly improved hypoxia tolerance by *HIF-1* signaling pathway in a multi-target way, and established targets for diseases and drugs. Because of the lack of validation of the corresponding experiments, we may carry out in vitro and in vivo verification experiments.

Declarations

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Statement of conflict of interest

There is no conflict of interest in this study and all authors have read and approved the manuscript.

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Tables

Table 1

A partial information table for the core targets.

NO.	Drgree	Protein Target name
1	26	IL6
2	25	TNF
3	23	NOS3
4	23	CCL2
5	23	VEGFA
6	23	IL1B
7	22	TP53
8	22	IL10
9	21	EGFR
10	21	STAT3

Due to technical limitations, table 2 docx is only available as a download in the Supplemental Files section.

Figures

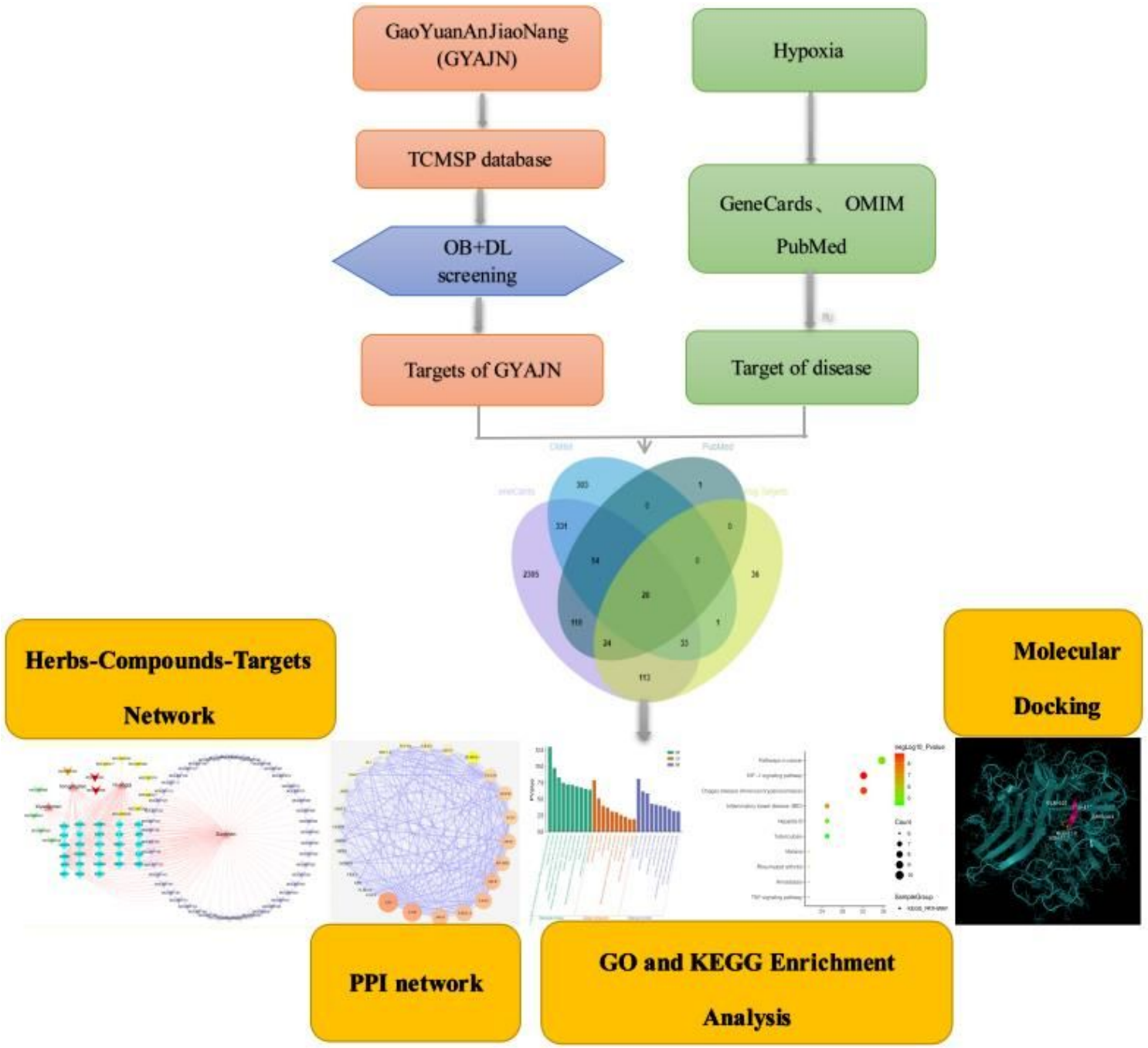

Figure 1

Flow chart of this research

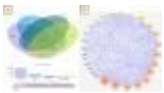

Figure 2

The Wain diagram was obtained by using EHBIO online mapping tool platform, as shown in Figure 2 A PPI network, as shown in Figure 2 B. Higher resolution image was not provided with this version.

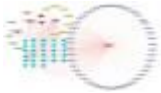

Figure 3

Cytoscape 3.7.2 was used to obtain the “Herb-compound-target” network diagram, there are 92 nodes and 245 edges, as shown in Figure 3. Higher resolution image was not provided with this version.

Figure 4

Enrichment analysis of GO function and KEGG pathway. Higher resolution image was not provided with this version.

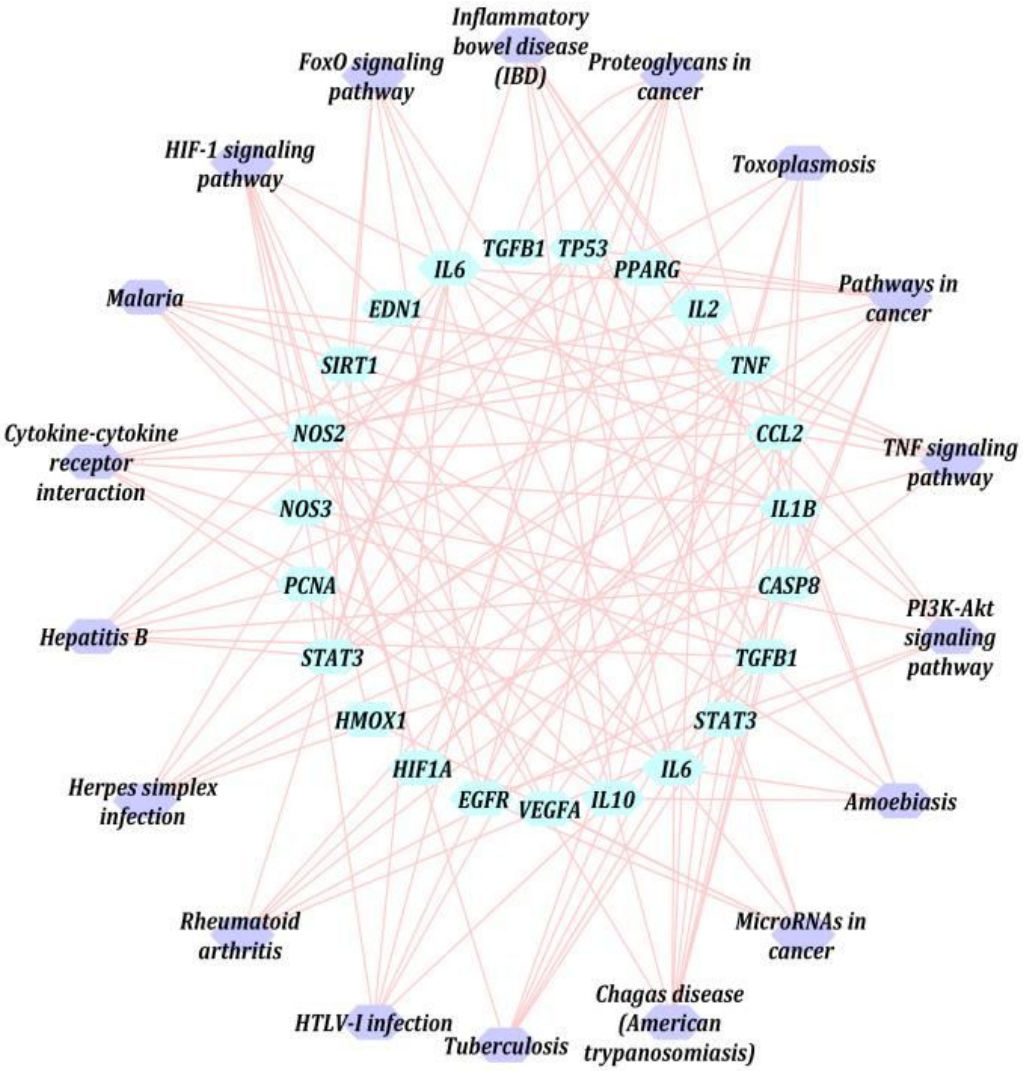

Figure 5

Target-pathway network

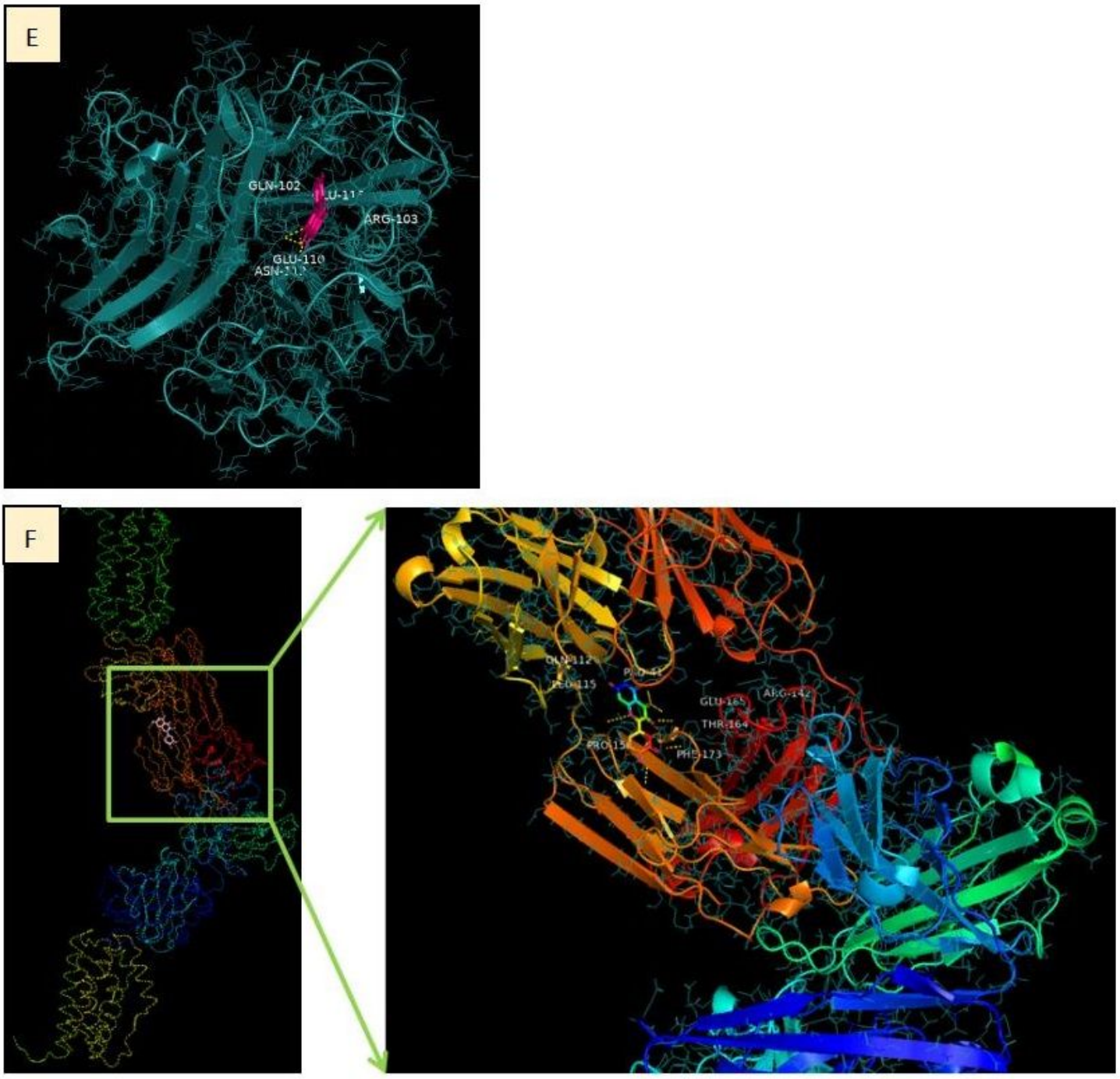

Figure 6

Molecular docking results

Supplementary Files

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