INTRODUCTION

Non-alcoholic fibre liver disease (NAFLD) means a series of illnesses from simple steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis, which has been thought to be a hepatic indication for metabolic syndromes. It is currently recognized as a commonly seen long-lasting and recurrent hepatic illness almost throughout the world, which is also most common for westerners. NAFLD has...
been proven by increasing studies as an indication of metabolic syndrome, with insulin resistance, hyperglycaemia and dyslipidaemia, and oxidative stress.\textsuperscript{2,3} Insulin resistance may be a commonly seen pathogenic event.\textsuperscript{4} According to the ‘parallel multiple-hit theory’,\textsuperscript{5} IR (insulin resistance), as an independent risk for NAFLD severity,\textsuperscript{6} is thought to be a ‘first blow’ triggering the illness, resulting in elevation of free fatty acids (FFAs) in hepatocytes.

In China, nowadays, the traditional Chinese medicine (TCM) has been made into practice for centuries. Increasing attention to it has been attracted because of its great effectiveness and minimal side effect upon preventing and treating metabolic disturbance, particularly in NAFLD.\textsuperscript{8,9} \textit{Gynostemma pentaphyllum} (Thunb), a plant belonging to the Cucurbitaceae family, has been mentioned in the books to have various therapeutic effects.\textsuperscript{7} In recent years, people have made systematic research on the chemical composition, pharmacology, clinical and health care development of Thunb. Thus far, acquisition of about 180 gypenosides is achieved out of G. pentaphyllum through isolation.\textsuperscript{10} In our previous studies, Thunb has been found to reduce insulin resistance in high-sugar mice;\textsuperscript{11} however, Thunb fails to get completely understood from its chemical composition and function mechanisms, so it is warranted to explore the potential mechanism of Thunb to improve insulin resistance in NAFLD.

NAFLD is regulated by multiple genes or targets. For single target highly selective ligands drugs often do not change the overall state of the disease, it is difficult to effectively control or prevent the development of disease; therefore, the outcomes of the clinical trials were not satisfactory. Morphy et al. provide a new idea for drug discovery: multi-target therapy.\textsuperscript{12} Exploration of drugs from multiple targets and multiple pathways offers an insight to develop new drugs. Network pharmacology functions as a big data integration approach upon the basis of large database resources and static algorithms, which is utilized for observing the interaction of multiple drug components, targets and disease mechanisms. It is also utilized for the prospective analysis of traditional Chinese medicine.\textsuperscript{12-14} Consequently, adoption of the network pharmacology method is conducted for investigating the latent therapeutic targets and pathways of Thunb during NAFLD treatment. NASH is a key process in the progression of NAFLD, so we also created a network to investigate the latent therapeutic targets and pathways of Thunb during NAFLD treatment. Molecular docking explorations are also done for further predicting the identification and interactive patterns amid Thunb as well as the targets predicted.

2 | MATERIALS AND METHODS

2.1 | Composite components of Thunb

The data of Thunb are mainly from a verified target databases: (1) pharmacology database of traditional Chinese medicine system\textsuperscript{15} (TCMSP, http://lsp.nwu.edu.cn/tcmsp.php).

2.2 | Screening of bioactive components

In the clinical application of Thunb, oral administration has been normally utilized in Chinese medicine. Therefore, these two ADME models of oral bioavailability (OB)\textsuperscript{16} and drug similarity (DL)\textsuperscript{17} become the primary variables producing impact upon drug absorption in the gastrointestinal tract.\textsuperscript{18} Hence, OB\textgreater{}30% and DL\textgreater{}0.18 should be employed as screening conditions for screening the bioactive components of Thunb. (OB works as an important index for the objective assessment of the oral bioavailability of drug molecules, while DL is an index for the assessment of drug molecular drugging).

2.3 | Prediction of Thunb action target

Currently, there are many methods to predict drug targets, according to its prediction principle, classification of those approaches into four types is performed:(1) Structure-based prediction approaches, which are based on the structural properties of compounds; (2) Molecular Activity-based prediction approaches.

| MOLID       | MolName                  | OB (%) | DL   |
|-------------|--------------------------|--------|------|
| MOL000338   | 3′-methyleriodictyol      | 51.61  | 0.27 |
| MOL000351   | Rhamnazin                | 47.14  | 0.34 |
| MOL000359   | Sitosterol               | 36.91  | 0.75 |
| MOL004350   | Ruvoside\textsubscript{qt}| 36.12  | 0.76 |
| MOL004355   | Spinasterol              | 42.98  | 0.76 |
| MOL005438   | Campesterol              | 37.58  | 0.71 |
| MOL005440   | Isofucosterol            | 43.78  | 0.76 |
| MOL007475   | Ginsenoside f2           | 36.43  | 0.25 |
| MOL009953   | CLR                      | 37.87  | 0.68 |
| MOL009998   | Quercetin                | 46.43  | 0.28 |
| MOL009855   | (24S)-Ethylcholesta-5,22,25-trans-3beta-ol | 46.91 | 0.76 |
| MOL009867   | 4α,14α-dimethyl-5α-ergosta-7,9(11),24(28)-trien-3β-ol | 46.29 | 0.76 |
| MOL009877   | cucurbita-5,24-dienol     | 44.02  | 0.74 |
| MOL009878   | Cyclobuxine              | 84.48  | 0.7  |
| MOL009888   | Gypenoside XXXVI\textsubscript{qt} | 37.85 | 0.78 |
| MOL009928   | Gypenoside LXXX IV       | 34.21  | 0.24 |
| MOL009929   | Gypenoside LXXX IX       | 37.75  | 0.25 |
| MOL009938   | Gypenoside XII           | 36.43  | 0.25 |
| MOL009943   | Gypenoside XL            | 30.89  | 0.21 |
| MOL009969   | Gypenoside XXXV\textsubscript{qt} | 37.73 | 0.78 |
| MOL009971   | Gypenoside XXVII\textsubscript{qt} | 30.21 | 0.74 |
| MOL009973   | Gypenoside XXVIII\textsubscript{qt} | 32.08 | 0.74 |
| MOL009976   | Gypenoside XXXII         | 34.24  | 0.25 |
| MOL009986   | Gypentonoside A\textsubscript{qt} | 36.13 | 0.8  |
FIGURE 1 (A) PPI network of NAFLD targets. (B) PPI network of NASH targets. The nodes range in size and colour from largeness to smallness, greenness to redness, according to descending sequence of extent.
which are upon the basis of the protein interaction network (PIN); (3) Side-effect-based prediction approaches upon the basis of the adverse reactions; (4) Multi-Omics-based predictions methods, upon the basis of the predicting theory that identical medication has action upon those identical targets. The exploration used TCMSP\textsuperscript{15} (http://lsp.nwu.edu.cn/tcmsp.php) and SymMap\textsuperscript{19} (https://www.symmap.org/), to predict these targets of Thunb components. Considering that every interaction put forward should possess traceability to the original information sources in this database.

2.4 NAFLD-related targets

Depending on the features of every database, this exploration chose to use distinctive keywords and standards to retrieve NAFLD-related targets. 'non-alcoholic fibre liver disease/ non-alcoholic steatohepatitis' should be utilized to be a keyword in searching the Drugbank database\textsuperscript{20} (http://www.drugbank.ca). 'Non-alcoholic fibre liver disease/ non-alcoholic steatohepatitis' should be utilized to be a keyword in searching the GeneCards\textsuperscript{21} (http://www.genecards.org/).
2.5 | Protein–protein interaction analysis

The normal life activities of cells are inseparable from the interaction of proteins and other molecules, like genes, small molecule compounds and other proteins. A complete organism interaction set can be shown through a PPI network, in which a single protein is thought to be a node, while a pair of proteins have a physical interaction as an edge. On the String, the identifiers meant ‘Homo sapiens, multiple proteins’; the data sources of PPI were chosen. After that, construction of PPI networks for targets in relation to NAFLD/NASH and Thunb was done. Identification of essential targets in anti-NAFLD and anti-NASH system should be performed through utilization of network data for topology features analyses.

2.6 | Gene ontology and KEGG analysis

As a reference knowledge base, KEGG can be utilized to interpret massive molecular data sets from biology, like genome and metagenome sequences. It has accumulated experimental knowledge of...
advanced functions of cells and organisms represented by KEGG molecular network, comprising KEGG pathway diagram, Brite hierarchy and KEGG module.\textsuperscript{24} For revealing the latent mechanism of Thunb treatment for NAFLD and NASH, the overlapping targets had been introduced into the Database for Integrated Discovery, Visualization and Annotation, DAVID 6.8\textsuperscript{25} (http://david.ncifcrf.gov/), for performing KEGG pathway analyses and GO functional analyses. Functional annotation of enrichment was performed by Benjamini correction (P<0.05). KEGG pathway enrichment maps and GO enrichment were performed under R version 3.2.0.

2.7 | Network construction

Using Cytoscape3.6.1\textsuperscript{26} (http://cytoscape.org) as the biomolecular interaction network integration model of software environment, the following were built: (1) the compound-target network; (2) PPI network of compound-NAFLD/compound-NASH target; and (3) compound-target-pathway network.

Three metrics had been utilized for evaluating the topology features for every node. (1) ‘Betweenness Centrality’: The ratio of nodes has the shortest path through the network;\textsuperscript{27} (2) ‘Closeness Centrality’ serves as a reflection on the distance amid one node and another one;\textsuperscript{28} (3) ‘Degree’ means the quantity of nodes that have direct relation with these nodes within this network.\textsuperscript{29} Level of the three parameters gives a reflection on the significance of those nodes within the network topology, the higher the value node, the more important.

2.8 | Molecular docking simulation

2.8.1 | Target protein preparation

Downloading of the crystal structures for hub genes was made out of RCSB Protein Data Bank\textsuperscript{30} (http://www.pdb.org/). Modification of those complexes already downloaded was done through utilizing the AutoDock Tools 1.5.6\textsuperscript{31} (http://mgltools.scripps.edu/documentation/links/autodock) for removing the water molecules, which had been utilized for preparing receptors, comprising the addition of hydrogen and set-up of docking parameters. Upon maximizing the settings, ‘Grid box’ had been utilized for performing the subsequent docking.

2.8.2 | Ligand preparation

Prior to docking, we downloaded the 3D structure of Thunb from TCMSP (https://tcmspw.com/tcmsp.php) and applied minimum energy to do subsequent docking.

2.8.3 | Molecular docking

We saved every ligand and receptor file in pdbqt format. After that, Autodock Vina was utilized,\textsuperscript{32} which is an open-source package with great availability for free, for evaluating and verifying the binding affinity for compound-target relation. With utilization of PyMol2.3.0 software, visualization of the binding models was realized.

3 | RESULTS

3.1 | Screening of Thunb active ingredients

In line with the above retrieval standards (OL≥30% DL≥0.18), altogether, 24 active constituents had been screened, and Table 1 below reveals their basic information.

3.2 | NAFLD target network

According to Figure 1A, the PPI network gave a reflection on the interactive statuses amid the total of 937 targets, which had been recorded as the disease potential targets of NAFLD. As for the node degree, six targets were highly correlated with the pathological process of NAFLD, including INS (insulin, degree = 453), IL6 (interleukin-6, degree = 400), AKT1 (RAC-alpha serine/threonine-protein kinase, degree = 382), ALB (albumin, degree = 375), TP53 (tumour protein p53, degree = 349) and TNF (tumour necrosis factor, degree =339). In addition according to relevance score >0.5, there is the total of 208 targets had been recorded as the disease potential targets of NASH.

3.3 | PPI network of compound-NAFLD/compound-NASH targets

Upon the basis of outcomes hereinabove, the 150 assumed targets of Thunb were mapped to 937 NAFLD-related targets for obtaining overlapping targets. Thus, 84 targets had been confirmed to be candidates for the treatment of NAFLD (Figure 2A) and 91 targets had been confirmed to be candidates for the treatment of NASH. Then, a PPI network should be built up for evaluating the function of those targets among complex diseases and found that the interaction between them. The topology characteristics of PPI network had been analysed, and sorting of 84 targets into descending sequence was conducted. In Figure 2B, nodes according to the degree are arranged into concentric circles, centre of the innermost circle consists of 11 nodes, including AKT1, IL6 (interleukin-6), VEGFA (vascular endothelial growth factor A), JUN (transcription factor AP-1), PTGS2.
(prostaglandin-endoperoxide synthase 2), CXCL8 (interleukin-8), MMP9 (matrix metallopeptidase 9), CASP3 (caspase-3), IL1B (interleukin-1 beta) and CCL2 (monocyte chemotactic protein [MCP]-1).

3.4 | GO and KEGG pathway analysis

For additionally expounding the mechanism of drug therapy in a systematical manner, utilization of DAVID had been done for performing enrichment analyses of genes. The top10 KEGG pathways and GO items were selected according to gene count and P value. According to the findings from biological processes, the targets were enriched in negatively regulated apoptotic process (GO:0043066), signal transduction (GO:0007165), positively regulated apoptotic process (GO:0043065), response to insulin (GO:0032868) and glucose metabolic process (GO:0006006) (Figure 3A,C). A total of 99 pathways were obtained by KEGG analyses, and majority got involvement with insulin resistance and apoptotic process-related pathways like P13K–AKT signalling pathway (hsa04056), non-alcoholic fatty liver disease (NAFLD) (hsa04045), insulin resistance (hsa04046) and apoptosis (hsa04067). In this study, we investigated the potential interaction activities between 13 hub genes of Thunb and their relevant compounds by molecular docking verification. Meanwhile, the docking affinity values were obtained by Autodock Vina and utilized for further screening the retrieved targets and active compounds. A total of 15 pairs were delivered to the docking simulation (Table 2). In the docking outcomes, a majority of the binding possessed great binding affinity, whose mean value was −5.97 kcal/mol. The modes of 3 binding complexes are shown in Figure 4, such as GSK3B-Rhamnazin docking (−5.82 kcal/mol), AKT-Quercetin docking (−6.36 kcal/mol) and INSR-Quercetin docking (−6.85 kcal/mol). When the docking affinity possesses higher absolute values, a stronger binding capability was seen in these compounds to the target active site. Specifically, taking the INSR-Quercetin docking as an example, small molecule ligand Quercetin may be suitable for the interface pocket under the formation of interacted amino acid residues in the protein (Figure 4). It revealed five hydrogen bonds were formed amid ligand and residues in MET 1079, ASP 1150 and LEU 1002. Five hydrogen bond interactions were 1.9, 2.0, 2.1, 2.1 and 2.2Å, respectively, which were considered as strong interactions. Overall, we found that different interactive forms would make a determination on the capability of binding affinity, and the hydrogen bond was the primary forms of interactive statuses for 3 docking complexes.

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4 | DISCUSSION

Recently, an increasing quantity of explorations had been conducted in medication discovery and combination therapy of traditional Chinese medicine for complex diseases such as NAFLD, among which network pharmacological methods have played an important role. The multiply components and multiply target features of traditional Chinese medicine make it possible to control symptoms through different biological processes and effectively prevent the deterioration of the disease. In this exploration, construction of a network hereinbelow was done for revealing the latent targets and pathways of Thunb during NAFLD/NASH treatment.

Upon integration and consolidation of data out of multiple accessible databases, 4 active compounds of Thunb had action upon 84 different targets in association with NAFLD and 91 different targets in association with NASH. Our previous studies have shown that Thunb can reduce insulin resistance in NAFLD, however, its bioactive components and mechanisms of action have not been identified. Therefore, network pharmacology was utilized for screening the active components and targets of Thunb; the potential mechanism of Thunb was also acquired to reduce insulin resistance in NAFLD. The PPI network of NAFLD targets gave a reflection of the latent targets and pathways of Thunb during NAFLD/NASH treatment.

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A widely reported viewpoint rests with that insulin resistance has a central function during those procedures through permitting too much fatty acid to flow into adipose tissue and impairing the disposal of peripheral glucose. FFAs are absorbed by the liver in proportion to their delivery rate and have a direct stimulation upon the synthesis of very low-density lipoprotein (VLDL). When these FFAs get absorbed by hepatocytes, they will temporarily be stored as triglycerides and then be released as VLDL particles. In addition, due to excessive carbohydrates, like fructose, another significant contributor to the hepatocyte triglyceride pool refers to de novo adipogenesis. Three main sites of insulin resistance include the muscle, liver and adipose tissue. Insulin resistance...
has been considered to begin in muscle tissue, with inflammation alteration under the mediation of immune and excessive FFAs, resulting in ectopic lipid deposition. Muscles account for 70% of glucose disposal. As muscle uptake is impaired, excessive glucose is back to the liver elevating de novo lipogenesis and circulating free fatty acids. When the delivery of these energy substrates exceeds the capacity of the liver to process them, the triglyceride pool will continue to grow. These FFA metabolites result in liver cell damage characterized by endoplasmic reticulum stress, apoptosis, inflammation, necrosis and deformities like balloon and Mallory–Denk body formation.

As is universally known, P13K/Akt/GSK3β pathway functions as one of the most important insulin signalling pathways. Massive proof indicated the direct increase in de novo lipogenesis by deregulated P13K/Akt/GSK3β signalling pathway and indirect elevation of FFA flux to the liver through the increase in adipose tissue lipolysis. (Figure 5) Meantime, molecular docking simulation amid 26 hub genes and 4 active compounds were conducted for complementing key targets. These outcomes revealed the good docking affinity for each target–compound pairs possess, particularly GSK-3β and AKT1 (Figure 5).

Glycogen synthase kinase-3 (GSK-3) serves as a post-insulin receptor signalling protein. There are two isomers, GSK-3β and GSK-3α, which are inactivated when phosphoric acid is added and activated when phosphoric acid is deactivated. Under normal circumstances, insulin inactivates GSK-3β by phosphorylating it, and the inactivated GSK-3β loses its inhibitory effect on liver glycogen, thus promoting the synthesis of liver glycogen. However, in type 2 diabetes mellitus, because of insulin resistance, the GSK-3β phosphorylation pathway is blocked, liver glycogen synthesis is inhibited, and liver glycogen content decreases, resulting in increased blood sugar concentration. The liver P13K/AKT signalling pathway is the most important and classic pathway for the regulation of gsk-3 activity. Under normal circumstances, after insulin binding to the insulin receptor, the insulin receptor substrates (IRSs) are phosphorylated and activate phosphatidylinositol-3 kinase (PI3K) by binding to the Src homology 2 (SH2) domain. Activated PI3K phosphorylates phosphatidylinositol diphosphate (PIP2) to form phosphatidylinositol triphosphate (PIP3). PIP3 recruits and activates phosphatidylinositol-dependent protein kinase 1 (PKD1) and protein kinase B (AKT). AKT inactivates glycogen synthase kinase-3β (GSK-3β) via Ser 9 phosphorylation. Heptic glycogen syn-
thesis are increased and blood glucose level drops. According to this exploration, the PPI network and the result of KEGG showed the effect of Thunb on INSR/AKT/GSK-3β. In addition, the results of compound-NASH showed the importance of P13K–AKT pathway in NASH. Therefore, it can be summarized from the results that the P13K–AKT signalling pathway has an important function in NAFLD, and intervening the process might become a latent therapeutic target for Thunb against NAFLD.
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