Original Research Article

In silico screening of potentially bioactive-anti-functional dyspepsia constituents of Magnoliae officinalis Cortex based on molecular docking and network pharmacology

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Abstract

Purpose: To screen for bioactive anti-functional dyspepsia compounds from Magnoliae officinalis Cortex (Hou Po) and to identify the mechanism(s) of action involved.

Methods: The compounds of Hou Po were collected from the literature. The related target proteins were identified from DrugBank. Through “Libdock” module of Discovery Studio 3.5, the compounds were matched with related target proteins. Taking the Libdock score of the original ligand with target protein as standard, components with higher scores than this standard were considered as potential bioactive compounds. Based on Cytoscape software, the interaction networks of the bioactive compound-target protein complexes were mapped. On the other hand, the online DAVID database was used to analyze the GO enrichment and KEGG pathway of each target.

Results: A total of 199 chemical constituents and 13 correlated target proteins were obtained. One hundred and thirty-nine (139) potential bioactive constituents were acquired based on molecular docking. Thirty-one (31) bioactive compounds were selected based on degree values in network analysis. “Palmitone” and “magnolignan G” which had the highest degree values were considered promising and leading compounds. The result of gene enrichment analysis showed that the bioactive compounds exerted their effects mainly via “neuroactive ligand-receptor interaction” pathway and “Cholinergic synapse” pathways.

Conclusion: Based on molecular docking and network pharmacology technique, the material basis for the use of Hou Po in the treatment of FD has been revealed. This finding provides a useful guide in the development of Hou Po-based anti-FD drugs.

Keywords: Magnolia officinalis, Hou Po, Molecular docking, Functional dyspepsia, Network pharmacology

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INTRODUCTION

Hou Po, classified under “resolving dampness with aromatics” in Chinese herbal medicine, is derived from the dried bark of the dried bark of Magnolia officinalis Rehd. et Wils. or Magnolia officinalis Rehd. et Wils. var. biloba Rehd. et Wils. The use of Hou Po in China has a long
history. It was first recorded in “Shen Nong’s herbal Classic” 2000 years ago. The ancient book recorded that Hou Po has the effect of treating abdominal pain and distension, as well as nausea and vomiting.

Traditional Chinese medicine prescriptions containing Hou Po have good therapeutic effects on diseases of the digestive system in clinics. Ban Xia-Hou Po decoction on functional dyspepsia (FD) patients showed that it effectively reduced abdominal bloating [1]. In addition, results from systems pharmacology analysis on Huo-Xiang-Zheng-Qi decoction revealed the mechanism involved in its therapeutic effect on gastrointestinal diseases [2]. Modern pharmacological have revealed that Hou Po has extensive pharmacological effects, including relief of abdominal distension, as well as anti-stress, anti-anxiety, anti-depressant, anti-inflammatory, and anti-oxidant properties [3, 4]. At present, Hou Po is still widely used in Asian countries [5].

There has been a significant decline in the rate of transformation of novel phytochemicals from traditional Chinese medicine (TCM) to effective drugs, due to the high cost, long cycles, and complicated procedures involved. Interestingly, molecular docking, an advancement in, computer technology, has enhanced the study of bioactive components of TCM. Molecular docking is a computer-based technique for identifying the binding abilities of candidate compounds to target proteins with known structures [6]. Nowadays, increasing research has shown that molecular docking is a good strategy for the discovery and development of drugs from candidate compounds [7]. In general, molecular docking is combined with network pharmacology. The network pharmacology technology was introduced by Hopkins firstly, who used it to screen potential bioactive compounds and reveal the mechanism of action of multiple-component drugs [8].

Although clinical trials have shown that Hou Po is effective against FD, the mechanism of action of the drug is unknown. In the present study, molecular docking was successfully used to screen potentially bioactive anti-FD compounds from Hou Po. Based on results of molecular docking, network pharmacology was performed to screen the key potentially active compounds and to preliminarily reveal the mechanism underlying of its anti-FD effect.

**METHODS**

**Building of chemical component database**

Chemical compounds from Hou Po were obtained from the literature via CNKI.net (https://www.cnki.net/) and PubMed (https://pubmed.ncbi.nlm.nih.gov/) [4,9]. The chemical structures of the compounds were searched from SciFinder (http://sso.cas.org) or Chemical Book (http://www.chemicalbook.com), while their two-dimensional (2D) structures were sketched using Chem Sketch (version12.0), and saved as “mol” format.

**Target fishing**

First, the phrase, “Functional Dyspepsia”, was searched in DrugBank database (https://www.drugbank.ca/) to obtain the target proteins. Then, the 3D structures of the target proteins were acquired from RCSB Protein Data Bank (PDB, http://www.pdb.org/). Finally, the available target proteins were screened according to “Homo sapiens” setting, along with the crystal structures with ligands.

**Molecular docking**

**Active site preparation**

Based on Accelrys Discovery Studio 3.5 (DS 3.5), LibDock was used to carry out high-throughput screening. Each target protein was prepared through removal of water, addition of polar hydrogen, supplementation of incomplete amino acid residues, cleaning of protein, and removal of the poly-conformation [10]. Residues around the original ligands in the crystal structure were selected as the active site of protein and defined as a sphere. The radii of spheres were set at 5 Å. Then, original ligands in the sphere were removed. The active amino acid residues were set as a pocket. Other parameters were set as default [11].

**Ligand preparation**

The compounds were imported and the protocol “Prepare Ligands” was used to remove duplicates and enumerate isomers or tautomer of all compounds. The ligands were generated in their three-dimensional (3D) forms.

**Docking**

The LibDock module was used for docking the prepared target proteins and prepared ligands with default parameter. LibDock score was used to evaluate affinity of binding of the
compounds (ligands) to the proteins. Taking the Libdock score of the original ligand with target protein as standard, components with higher scores than this standard were considered as potentially bioactive compounds.

Construction of ligand-target network and screening bioactive compounds

Based on results of molecular docking, visual networks showing correlation of compounds with target proteins were established using Cytoscape software (3.7.2). The “degree” value in the network represented the numbers of compounds docking with the target proteins. The higher the “degree” values, the larger the shape. Constituents with degree value greater than or equal to 6 are regarded as bioactive compounds.

Target gene analysis

To illustrate the potential biological effects of target proteins, Gene Ontology (GO) attached to the DAVID was used to achieve gene enrichment. The GO database describes three aspects of the gene of target proteins: molecular function (MF), biological process (BP), cellular components (CC). The parameters were set with count ≥ 3 and p-value ≤ 0.001[12]. Besides, Kyoto Encyclopedia of Gene and Genomes database (KEGG) was employed for screening for pathways that met the criterion of count ≥ 2 and p-value ≤ 0.001.

RESULTS

Chemical component database and target proteins information

The compound database consisted of 199 compounds (C1-C199) comprising 82 lignans, 40 glycosides (phenylethanoid and phenolic glycosides), 26 alkaloids, 15 volatile oils, 6 flavonoids, and 30 others. 13 target proteins, involved dopamine receptors, serotonin receptors, acetylcholine receptors, and related enzymes, were obtained from the DrugBank database. Details of the 13 target proteins are shown in Table 1.

Molecular docking results

A total of 139 potentially bioactive compounds were obtained via DS 3.5 using the “LibDock” module. When a compound docked to the target protein, the interaction between the compound and amino acid residues generated hydrogen bonding and conjugation effects. The binding modes of some bioactive compounds with high LibDock scores are shown in Figure 1.

Table 1: Information about 13 target proteins

| No. | PDB ID | Target                                      | Abbreviation | Gene ID |
|-----|--------|---------------------------------------------|--------------|---------|
| 1   | 6CM4   | Dopamine D2                                 | DRD2         | 1813    |
| 2   | 3PBL   | Dopamine D3                                 | DRD3         | 1814    |
| 3   | 5CXV   | M1 muscarinic acetylcholine receptor         | CHRM1        | 1128    |
| 4   | 3UON   | M2 muscarinic acetylcholine receptor         | CHRM2        | 1129    |
| 5   | 5DSG   | M4 muscarinic acetylcholine receptor         | CHRM4        | 1132    |
| 6   | 5TVN   | Serotonin 5-HT2B                            | HTR2B        | 3357    |
| 7   | 4DJH   | Human kappa opioid receptor                 | OPRK1        | 4986    |
| 8   | 4IAR   | Serotonin 5-HT1B                            | HTR1B        | 3351    |
| 9   | 3N7R   | Calcitonin gene related peptide receptor    | CALCRL       | 10203   |
| 10  | 4BDT   | Phosphodiesterase 4                         | ACHE         | 43      |
| 11  | 4A79   | monoamine oxidase                           | MAOB         | 4129    |
| 12  | 4K5Y   | Corticotropin-releasing factor 1             | CRHR1        | 1394    |
| 13  | 3O5X   | Tyrosine phosphatase                        | PTPN11       | 5781    |

Figure 1: 2D and 3D ligand-protein interaction of high score compounds: (A-B) “magnolignan G” with “Calcitonin gene related peptide receptor” (PDB ID: 3N7R); (C-D) “magnoloside G” with “serotonin 5-HT2B” (PDB ID: 5TVN)
Compound-target network and bioactive compounds

The network was constructed using 139 potentially bioactive compounds and 13 target proteins are shown in Figure 2. Compounds with degrees greater than or equal to 6 are listed in Table 2, along with their LibDock scores. “Palmitone” and “magnolignan G” had the highest degree value (degree value = 8). Finally, a total of 31 key bioactive compounds were selected through virtual screening and network pharmacology.

Figure 2: The “compound-target” network of Hou Po

Gene enrichment analysis

Gene Ontology (GO) was used to describe the genes in three aspects: molecular function, biological process, and cellular components. The results showed that these genes were enriched to 15 biological process terms, including “G-protein coupled receptor internalization, adenylate cyclase-inhibiting G-protein coupled acetylcholine receptor signaling pathway”. Cellular components described the genes involved in “integral components of plasma membranes, synapse”, etc. The biological functions of the genes were described in terms of “molecular transducer activity” and “signal transducer activity” (Figure 3). The results of KEGG pathway enrichment analysis with KEGG suggested that 8 pathways were significantly signaling (p<0.1). The “neuroactive ligand-receptor interaction” pathway, “dopaminergic synapse” pathway, and “serotonergic synapse” pathway were obtained (Figure 4).

DISCUSSION

FD, a type of gastrointestinal disorder, is characterized by the presence of symptoms thought to originate in the gastroduodenal region, in the absence of any organic, systemic, or metabolic disease [13]. A review has shown that FD significantly impacts both the Eastern and the Western countries, with overall higher incidence (10 - 40%) in Western countries than in Asia (5 - 30%) [14]. The disease has negative impact on the life of patients. Many FD patients usually suffer from abdominal discomfort, pain, burning, early satiety, and bloating [15]. These discomforts could be relieved by promoting gastric motility, reducing gastrointestinal sensitivity, treating gastroduodenal inflammation, regulating emotions, and using appropriate diet. However, enhancement gastrointestinal motility is the main treatment strategy for FD. Unfortunately, with time, the use of drugs that enhance promoting gastrointestinal motility leads to undesirable side effects. Some of these drugs e.g. domperidone, have been banned in the USA, Canada, and other counties [16-20]. Thus, it is crucial to identify novel candidate drugs for treating FD.

In this manuscript, “palmitone” and “magnolignan G” were identified as bioactive components with high degree value. However, there is no direct evidence on the treatment of FD with “palmitone” and “magnolignan G”. Interestingly, it has been reported that “palmitone” had a good effect on anxiety and depression [21]. Emotion is one of the causes of FD. Therefore, “palmitone” may be used to treat FD patients through regulation emotions.

The results of this study suggest that attention should be paid to “palmitone” and “magnolignan G”. It has been reported that phenylethanoid glycosides in Hou Po contribute significantly to the treatment of FD. “Mmagnoloside A” (degree value = 7), one of the phenylglycoside glycosides, has a positive effect on abdominal distention, pain, and dyspepsia [22]. A literature report indicated that “quercitrin” (degree value = 6) regulated gastrointestinal smooth muscle [23].

In this study, the results from molecular docking and network pharmacology, suggest that the bioactive components of Hou Po exert anti-FD effect by regulating “serotonin 5-HT2B receptor” (PDB ID: 5TVN), “corticotrophin-releasing factor 1 receptor” (PDB ID: 4K5Y), “dopamine D3 receptor” (PDB ID: 3PBL), “calcitonin gene-related peptide receptor” (PDB ID: 3N7R), and “Phosphodiesterase 4” (PDB ID: 4BDT). Furthermore, another pathway likely to be
### Table 2: Degree and Libdock scores of 31 bioactive compounds from *Hou Po*

| NO. | Compound                                                                 | 6CM L | 3PB L | 5CXV N | 3UO N | 5DS G | 5TVN H | 4DJ H | 4IAR T | 3N7 R | 4BD T | 4A7 9 | 4K5 Y | 3O5 X | Degree |
|-----|---------------------------------------------------------------------------|--------|-------|--------|-------|-------|--------|-------|--------|-------|-------|-------|-------|-------|--------|--------|
| C140| Palmitone                                                                 | 152    | 121   | 161    | 149   | 180   | 184    | 112   | 136    | 138   |       |       |       |       | 8      |
| C40 | Magnolignan G                                                             | 172    | 127   | 154    | 156   | 164   | 184    | 137   | 138    |       |       |       |       |       | 8      |
| C180| 3,4,5-trimethoxyphenyl β-D-apiofuranosyl (1→6)-β-D-glucopyranoside        | 109    | 153   | 157    | 132   | 158   | 154    | 116   | 7      |       |       |       |       |       | 7      |
| C179| 3,4-dimethoxyphenyl β-D-apiofuranosyl (1→6)-β-D-glucopyranoside           | 118    | 166   | 155    | 136   | 166   | 158    | 129   | 7      |       |       |       |       |       | 7      |
| C170| Pinoreinol-4-O-β-D-glucopyranoside                                        | 140    |       | 162    | 170   | 163   | 187    | 122   | 137    | 7      |       |       |       |       | 7      |
| C124| Choerospondin                                                             | 159    | 138   | 153    | 154   | 177   | 173    | 168   | 7      |       |       |       |       |       | 7      |
| C108| Magnofficine                                                              | 115    | 150   | 151    | 132   |       | 154    | 153   | 149    | 7      |       |       |       |       | 7      |
| C93 | Magnoloside Y                                                             | 169    | 152   | 189    | 165   | 174   | 204    |       | 144    | 7      |       |       |       |       | 7      |
| C92 | Magnoloside W                                                             | 176    | 133   | 164    | 171   | 182   | 201    |       | 149    | 7      |       |       |       |       | 7      |
| C83 | Magnoloside M                                                             | 185    | 149   | 169    | 159   | 185   | 208    |       | 143    | 7      |       |       |       |       | 7      |
| C79 | Magnoloside G                                                             | 163    | 152   | 180    | 155   | 172   | 177    |       | 164    | 7      |       |       |       |       | 7      |
| C76 | Magnoloside E                                                             | 194    | 153   | 183    | 173   | 184   | 211    |       | 149    | 7      |       |       |       |       | 7      |
| C75 | Magnoloside D                                                             | 187    | 154   | 183    | 172   | 187   | 211    |       | 159    | 7      |       |       |       |       | 7      |
| C74 | Magnoloside A                                                             | 176    | 161   | 165    | 171   | 189   | 185    |       | 148    | 7      |       |       |       |       | 7      |
| C53 | Lariciresinol                                                             | 114    | 154   | 135    | 147   | 156   | 159    | 131   | 7      |       |       |       |       |       | 7      |
| C48 | Magnolignan H                                                             | 152    | 120   | 133    | 147   | 165   | 194    | 124   | 7      |       |       |       |       |       | 7      |
| C46 | Houpulin K                                                                | 166    | 115   | 169    | 150   | 164   | 189    | 111   | 7      |       |       |       |       |       | 7      |
| C41 | Magnolignan F                                                             | 158    | 132   | 170    | 149   | 204    |        | 142   | 135    | 7      |       |       |       |       | 7      |
| C169| Syringaresinol 4'-O-β-D-glucopyranoside                                    | 112    |       | 152    | 145   | 163   | 178    |       | 134    | 6      |       |       |       |       | 6      |
| C123| Isorhamnetin-3-O-β-D-glucoside                                           | 117    | 152   | 143    |       | 159   | 162    | 119   | 6      |       |       |       |       |       | 6      |
| C121| Quercitrin                                                                | 121    | 153   | 135    |       | 158   | 161    | 127   | 6      |       |       |       |       |       | 6      |
| C94 | 1, 1'-dibenzen-6', 8', 9'-trihydroxy-3-allyl-4-O-β-D-glucopyranoside       | 130    |       | 149    | 148   | 172    | 157    | 151   | 6      |       |       |       |       |       | 6      |
| C86 | Acteoside                                                                 | 149    |       | 182    | 162   | 181   | 194    |       | 155    | 6      |       |       |       |       | 6      |
| C80 | Magnoloside H                                                             | 192    | 148   | 197    | 191   | 239   |        | 170   | 6      |       |       |       |       |       | 6      |
| C55 | Liriolresinol A                                                           | 111    |       | 142    | 147   | 164   | 156    | 140   | 6      |       |       |       |       |       | 6      |
| C54 | Syringaresinol                                                            | 116    |       | 143    | 146   | 162   | 149    | 148   | 6      |       |       |       |       |       | 6      |
| C47 | Houpulin L                                                                | 155    | 135   | 154    | 157   | 181   | 122    | 6      |       |       |       |       |       |       | 6      |
| C43 | Houpulin B                                                                | 160    | 128   | 156    | 154   | 176   | 142    | 6      |       |       |       |       |       |       | 6      |
| C32 | Bornyl magnolol                                                           | 115    | 152   | 138    |       | 148   | 154    | 132   | 6      |       |       |       |       |       | 6      |
| C30 | Piperityl honokiol                                                        | 119    | 150   | 141    |       | 153   | 135    | 137   | 6      |       |       |       |       |       | 6      |
| C29 | Piperityl magnolol                                                        | 122    | 148   | 136    |       | 152   | 156    | 138   | 6      |       |       |       |       |       | 6      |
Figure 3: The analysis of GO for target genes.

Figure 4: Bubble chart of 8 signaling pathways linked to the anti-FD of Hou Po
involved in the treating of FD by Hou Po could be “Neuroactive ligand-receptor interaction pathway”, which has 10 target proteins. Hou Po has been used for thousands of years, with very little reported side effects. Therefore, the bioactive components of Hou Po could be candidates for development of new drugs against FD.

CONCLUSION

Molecular docking and network pharmacology have been successfully used to screen for bioactive anti-FD compounds in Hou Po. A total of 31 key bioactive compounds have been identified and selected. Gene enrichment analysis has also revealed the mechanism involved in the anti-FD effect of Hou Po. These findings are beneficial for generating new anti-FD drugs.

DECLARATIONS

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Conflict of interest

No conflicts of interest are associated with this work.

Contribution of authors

We declare that this work was performed by the authors named in this manuscript, and all liabilities on claims relating to the content of this article will be borne by them. Yingfang Wei, Fei long and Guanghua Lv conceived and designed the study. Meng Yang, Yusha Bai, and Longjing Wang collected the data. Jun He did the detailed experiments and wrote the manuscript. Yunbin Jiang modified the manuscript. All authors read and approved the manuscript for publication.

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