Pharmacophore Modelling, Molecular Docking and Virtual Screening for Histamine H1 Receptor Antagonists from Traditional Chinese Medicine

Xing Wang, Zhenzhen Ren, Yuhong Xiang, Yanling Zhang, and Yanjiang Qiao

Abstract—This investigation was performed to identify histamine H1-receptor antagonists from traditional Chinese medicine through virtual screening based on pharmacophore and molecular docking. First, the pharmacophore models were generated though ten known H1 receptor antagonists. The models were validated by a test database and shown to have good performance in external validation. The best pharmacophore was employed to screen Traditional Chinese Medicine Database, which resulting in a hit list of 421 compounds. Then, the hits were subjected to molecular docking for further refinement. An empirical scoring function was used to evaluate the affinity of the compounds and the target protein. Parts of compounds with high docking scores have been reported to have the related pharmacological activity in the literatures. The findings indicated that virtual screening based on pharmacophore and molecular docking can provide a helpful tool to reveal the active ingredients from Chinese herbs. It can be used for identification of novel H1 antagonists from Traditional Chinese Medicine.

Index Terms—Histamine H1-receptor, virtual screening, traditional chinese medicine, active natural ingredients identification.

I. INTRODUCTION

Histamine, an ubiquitous chemical messenger that released from a variety of cells, has a key physiological role in the control of gastric acid secretion and allergic disorders. The histamine receptors are a class of G protein-coupled receptors with histamine as their endogenous ligand [1]-[3]. There are four known histamine receptors: H1, H2, H3 and H4. Histamine mediates allergic and inflammatory responses mainly through histamine H1 receptors, so H1 receptor antagonists can provides a highly successful approach to controlling allergic reactions [4], [5]. The first-generation antihistamines, such as diphenhydramine, tripelennamine, chlorpheniramine and promethazine, are able to across the blood-brain barrier. This ability contributes to their main adverse effect of sedation at the same time. So the first-generation are quickly replaced by the second-generation, which are far more selective for peripheral histamine H1-receptors and have fewer side-effects compared to the first-generation agents. But they make people sleepy as well, so discovering novel and safe H1-receptor antagonists is an important task to do.

Traditional Chinese medicine (TCM) is an ancient practice that has been practiced and perfected over thousands of years. It often uses the herbal concoctions, which contain hundreds of compounds from different biosynthetic origin and different chemical scaffolds, to counter the symptoms of diseases. It’s an extremely important and difficult work to recognize the active ingredients from hundreds compounds. In this paper, a combined virtual screening based on ligand and structure was proposed to quest for potential H1 receptor antagonists from TCM. And the hits with high scores were analyzed through literatures.

II. MATERIALS AND METHODS

A. Compounds and Biological Data

Compounds 1~10, which can inhibit H1-receptor, were taken from the literatures [6]-[8] and served as the training set in the pharmacophore modeling. The structures and inhibitory activities of the compounds are listed in Fig. 1. The chemical structures were drawn in ISIS-Draw software and saved in SYBYL mol2 format. All the 2D structures were converted to 3D structures by SYBYL X-1.2 software.

B. Modeling Tool

The studies were performed with SYBYL X-1.2 package (Tripos Inc., USA) running on Red Hat Linux workstation. The GALAHAD module was used to generate the pharmacophore model of H1 antagonists, the UNITY module was used to perform a flex search for the potential antagonists based on the pharmacophore model and the Surflex-Dock (SFXC) module was used to perform molecular docking.

C. Pharmacophore Modeling

Genetic algorithm with linear assignment of hypermolecular alignment of datasets (GALAHAD) was used to generate the pharmacophore models. All the compounds in the training set were prepared by the following procedures: the structures were checked for bond orders, hydrogen atoms were added and a minimization procedure was implemented using the MMFF94 force-field. GALAHAD was run for 100 generations with a population size of 80. The rest of the parameters were set as default values. The generated models were evaluated by a test.

Manuscript received January 15, 2013; revised March 15, 2013. This work was supported by the Foundation of National Natural Science Foundation of China (No. 81173522) and National Key Technology R&D Program (No. 2008BAI51B01) in Beijing University of Chinese Medicine.

Y. H. Xiang is with Capital Normal University, Beijing 100048, China (e-mail: cnuxiangyh@163.com).

Y. J. Qiao is with Beijing University of Chinese Medicine, Beijing 100102, China (e-mail: yjqi@263.net).

DOI: 10.7763/IJBBB.2013.V3.251
database which composed 130 experimentally known H1 antagonists [9]-[21] and 340 non-active compounds picked out from MDL Drug Data Report (MDDR, Version 200712) database.

![Chemical structure of H1-receptor antagonists](image1)

**D. Model Evaluation and Virtual Screening**

The pharmacophore models were generated by GALAHAD and validated by the test database, several parameters were employed for model evaluation and calculated as follows:

\[ A\% = \frac{Ha}{A} \times 100\% \]

\[ Y\% = \frac{Ha}{Ht} \times 100\% \]

\[ N = \frac{Ha \times D}{Ht \times A} \]

\[ CAI = N \times A\% \]

Where, \( D \) is the total number of compounds in test database and \( A \) is the number of active compounds. \( Ht \) is the total number of hit compounds from test database and \( Ha \) is the number of active hit compounds from test database. \( A\% \) represents the ability to identify active compounds from test database, \( Y\% \) represents the proportion of active compounds in the hit compounds. \( N \), the index of effective identification, was used to evaluate the ability of the models to identify active compounds from the non-active compounds. \( CAI \), a comprehensive evaluation index, was used to determine which model is the best model. The model with the highest value of \( CAI \) is considered to be the best. The best model was used to screen Traditional Chinese Medicine Database (TCMD, Version 2009).

**E. Molecular Docking Studies**

The crystal structure of histamine H1 receptor (H1, 3.10 Å, 3RZE.pdb) was selected as the docking template. The ligand doxepin was extracted, crystallographic water molecules in the structure were removed, hydrogen atoms of modeled structure were added to define the correct configuration and tautomeric states. With the standard parameters, the modeled structure was energy-minimized using AMBER7 F99 force field with the Powell energy minimization algorithm, distance dependent dielectric function and current charges.

After extracting the binding ligand, the structure of H1 receptor was used for re-docking with doxepin, and the docking score was calculated to check the accuracy of the Surflex-Dock program. The default parameters, as implemented in the SYBYL X-1.2 software, were used.

The compounds hit by the pharmacophore generated were automatically docked into the binding site of H1 successively. A protomol-based method and an empirically derived scoring function was used to calculate the interaction of the ligands and H1 receptor. The scoring function includes hydrophobic, polar, repulsive, entropic, solvation and crash terms. High total score implies good binding capacity. The crash value represents the degree of inappropriate penetration by the ligand into the protein and of interpenetration (self-clash) between ligand atoms that are separated by rotatable bonds. A smaller crash value indicates a better ability to exclude the false positives screened. Polar represents the contribution of the polar interactions to the total score. The polar score is useful for excluding docking results that make no hydrogen bonds.

**III. RESULTS AND DISCUSSION**

**A. Pharmacophore Modelling**

Twenty GALAHAD models, generated by ten known H1 antagonists, were derived from more than seven ligands. Model 3, 9, 14, 19 and 20 had high energy (SE > 1.0×10⁸), which is considered to be due to steric clashes, leading to their exclusion from the analysis. The other 15 models were evaluated successively by the test database constructed previously. Table I shows the predictable results for each model. Model_017, with the highest value of CAI, was considered to be the best model.

![Pharmacophore model_017 and molecular alignment of the compounds](image2)
The pharmacophore features of Model_017 were displayed in Fig. 2, where cyan, green and magenta spheres indicate hydrophobes, HB acceptors and HB donors, respectively. Model_017 includes five pharmacophore features: three hydrophobes, one HB acceptors and one HB donors.

### TABLE I: THE PARAMETER VALUES FOR EACH PHARMACOPHORE MODEL

<table>
<thead>
<tr>
<th>Model</th>
<th>Ht</th>
<th>Ha</th>
<th>A%</th>
<th>Y%</th>
<th>N</th>
<th>CAI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>347</td>
<td>126</td>
<td>0.97</td>
<td>0.36</td>
<td>1.31</td>
<td>1.27</td>
</tr>
<tr>
<td>2</td>
<td>340</td>
<td>126</td>
<td>0.97</td>
<td>0.37</td>
<td>1.34</td>
<td>1.30</td>
</tr>
<tr>
<td>3</td>
<td>332</td>
<td>126</td>
<td>0.97</td>
<td>0.38</td>
<td>1.37</td>
<td>1.33</td>
</tr>
<tr>
<td>4</td>
<td>292</td>
<td>87</td>
<td>0.67</td>
<td>0.30</td>
<td>1.08</td>
<td>0.72</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>9</td>
<td>0.22</td>
<td>0.36</td>
<td>1.31</td>
<td>0.29</td>
</tr>
<tr>
<td>6</td>
<td>97</td>
<td>3</td>
<td>0.25</td>
<td>0.33</td>
<td>1.19</td>
<td>0.29</td>
</tr>
<tr>
<td>7</td>
<td>80</td>
<td>4</td>
<td>0.26</td>
<td>0.43</td>
<td>1.54</td>
<td>0.40</td>
</tr>
<tr>
<td>8</td>
<td>145</td>
<td>7</td>
<td>0.38</td>
<td>0.52</td>
<td>1.87</td>
<td>1.08</td>
</tr>
<tr>
<td>9</td>
<td>360</td>
<td>126</td>
<td>0.97</td>
<td>0.35</td>
<td>1.27</td>
<td>1.23</td>
</tr>
<tr>
<td>10</td>
<td>158</td>
<td>98</td>
<td>0.75</td>
<td>0.62</td>
<td>2.24</td>
<td>1.69</td>
</tr>
<tr>
<td>11</td>
<td>213</td>
<td>114</td>
<td>0.88</td>
<td>0.54</td>
<td>1.93</td>
<td>1.70</td>
</tr>
<tr>
<td>12</td>
<td>265</td>
<td>8</td>
<td>0.66</td>
<td>0.32</td>
<td>1.17</td>
<td>0.78</td>
</tr>
<tr>
<td>13</td>
<td>154</td>
<td>7</td>
<td>0.75</td>
<td>0.63</td>
<td>2.28</td>
<td>1.70</td>
</tr>
<tr>
<td>14</td>
<td>352</td>
<td>126</td>
<td>0.97</td>
<td>0.36</td>
<td>1.29</td>
<td>1.25</td>
</tr>
</tbody>
</table>

B. Virtual Screening

Model_017 was used to screen TCMD, which contains 23033 natural chemical compositions. A query fit (QFIT) value was computed for each hit to rank the matching rate of its required structural features on the pharmacophoric query, a high QFIT score corresponds to a good alignment between pharmacophore model and compound conformer. Virtual screening based on pharmacophore was performed resulting in a hit list of 421 compounds. According to the QFIT values, the top 20 compounds are listed in Table II, and the best compounds mapping on Model_017 are shown in Fig. 3. Then, the compounds were subjected to molecular docking for further refinement.

![Fig. 3. Model_017 mapped with a) Pakistanamine and b) Pseudocarpaine.](image)

C. Molecular Docking

All the hits were docked into the active site of H1 receptor. The docking reliability was validated by re-docking the ligand extracted and the structure of H1 receptor. The low root mean-square deviation (RMSD) of 0.56 Å between the docked and the crystal conformation of doxepin indicated the high reliability of Surflex-dock in reproducing the experimentally observed binding mode for H1 inhibitor.

### TABLE II: THE TOP 20 COMPOUNDS HIT BY PHARMACOPHORE MODEL _017_

<table>
<thead>
<tr>
<th>No</th>
<th>ID</th>
<th>QFIT</th>
<th>name</th>
<th>source plant</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16537</td>
<td>72.5</td>
<td>Pakistanamine</td>
<td>Berberis calliobrytys and Berberis julianae</td>
</tr>
<tr>
<td>2</td>
<td>3218</td>
<td>61.21</td>
<td>Pseudocarpaine</td>
<td>Carica papaya.</td>
</tr>
<tr>
<td>3</td>
<td>18022</td>
<td>61.21</td>
<td>Carpine</td>
<td>Carica papaya.</td>
</tr>
<tr>
<td>4</td>
<td>11640</td>
<td>60.93</td>
<td>Isopyruthaldine</td>
<td>Isopyrum thalictroides</td>
</tr>
<tr>
<td>5</td>
<td>20933</td>
<td>60.27</td>
<td>Tenuicausine</td>
<td>Melodinus tenuicaudatus.</td>
</tr>
<tr>
<td>6</td>
<td>19592</td>
<td>58.93</td>
<td>Scutianine D</td>
<td>Scutia baxifolia</td>
</tr>
<tr>
<td>7</td>
<td>21269</td>
<td>58.07</td>
<td>Thalrugossidine</td>
<td>Thalictrum alpinum</td>
</tr>
<tr>
<td>8</td>
<td>12861</td>
<td>56.74</td>
<td>Lindechunine B</td>
<td>Lindera chunii</td>
</tr>
<tr>
<td>9</td>
<td>648</td>
<td>56.4</td>
<td>Adouetine X</td>
<td>Waltheria americana.</td>
</tr>
<tr>
<td>10</td>
<td>2456</td>
<td>56.2</td>
<td>2”,6”-Bis(p-hydroxybenzyl)-3,3’-dihydroxy-5-methoxybibenzyl</td>
<td>Gymnadenia conopsea</td>
</tr>
<tr>
<td>11</td>
<td>3882</td>
<td>54.47</td>
<td>Cocscule</td>
<td>Cocculus pendulas.</td>
</tr>
<tr>
<td>12</td>
<td>22596</td>
<td>54.22</td>
<td>Voacamine</td>
<td>family Apocynaceae spp.</td>
</tr>
<tr>
<td>13</td>
<td>2106</td>
<td>53.83</td>
<td>Baicalin</td>
<td>Scutellaria baicalensis</td>
</tr>
<tr>
<td>14</td>
<td>5099</td>
<td>52.87</td>
<td>De-O-methylhenaicausine</td>
<td>Melodinus hempleyanus.</td>
</tr>
<tr>
<td>15</td>
<td>14410</td>
<td>52.54</td>
<td>O-12’-Methyl ergocornine</td>
<td>Claviceps purpurea.</td>
</tr>
<tr>
<td>16</td>
<td>12564</td>
<td>52.44</td>
<td>Launobine</td>
<td>Lindera umbellata and Laurus nobilts</td>
</tr>
<tr>
<td>17</td>
<td>21244</td>
<td>52.24</td>
<td>Thalicrine</td>
<td>Thalictrum thunbergii</td>
</tr>
<tr>
<td>18</td>
<td>9444</td>
<td>50.73</td>
<td>Hernandine</td>
<td>Lindera chunii</td>
</tr>
<tr>
<td>19</td>
<td>6315</td>
<td>49.84</td>
<td>Giraldine G</td>
<td>Delphinium giraldii</td>
</tr>
<tr>
<td>20</td>
<td>2102</td>
<td>49.56</td>
<td>Baicalein</td>
<td>Scutellaria baicalensis</td>
</tr>
</tbody>
</table>

The compounds hit by pharmacophore model were docked into the active pocket of H1 receptor successively. The docking score was calculated by an empirically derived scoring function that is based on the binding affinities of protein-ligand complexes. 24 compounds with high docking scores were shown in Table III. The interactions between...
Baicalin and active site of H1 receptor is shown in Fig. 4.

**Fig. 4.** The interactions between Baicalin and active site of H1 receptor. Key residues are displayed and hydrogen bonds are displayed in dotted lines. a) 2D concise schematic diagram of the interactions between Baicalin and H1 receptor. b) MOLCAD lipophilic potential surface of the binding pockets with the docked compound Baicalin.

<table>
<thead>
<tr>
<th>Name</th>
<th>Total_Score</th>
<th>Crash</th>
<th>Polar</th>
</tr>
</thead>
<tbody>
<tr>
<td>9102</td>
<td>10.173</td>
<td>-1.3262</td>
<td>0.0003</td>
</tr>
<tr>
<td>12683</td>
<td>9.5702</td>
<td>-3.3676</td>
<td>2.6081</td>
</tr>
<tr>
<td>12891</td>
<td>9.5168</td>
<td>-1.7739</td>
<td>2.0805</td>
</tr>
<tr>
<td>5905</td>
<td>7.9974</td>
<td>-3.5484</td>
<td>2.4087</td>
</tr>
<tr>
<td>14154</td>
<td>7.5825</td>
<td>-1.1533</td>
<td>1.0442</td>
</tr>
<tr>
<td>18790</td>
<td>7.1964</td>
<td>-1.069</td>
<td>2.9856</td>
</tr>
<tr>
<td>23</td>
<td>7.1412</td>
<td>-1.2142</td>
<td>0.0139</td>
</tr>
<tr>
<td>2106</td>
<td>7.1296</td>
<td>-3.6908</td>
<td>3.1928</td>
</tr>
<tr>
<td>4417</td>
<td>6.9752</td>
<td>-0.7217</td>
<td>0.9007</td>
</tr>
<tr>
<td>16268</td>
<td>6.9716</td>
<td>-4.3417</td>
<td>1.1258</td>
</tr>
<tr>
<td>2165</td>
<td>6.8233</td>
<td>-0.6496</td>
<td>1.288</td>
</tr>
<tr>
<td>9100</td>
<td>6.4317</td>
<td>-4.0569</td>
<td>2.7437</td>
</tr>
<tr>
<td>1838</td>
<td>6.374</td>
<td>-2.3313</td>
<td>1.044</td>
</tr>
<tr>
<td>14995</td>
<td>6.2569</td>
<td>-6.9532</td>
<td>2.4127</td>
</tr>
<tr>
<td>6853</td>
<td>6.146</td>
<td>-0.7035</td>
<td>1.2522</td>
</tr>
<tr>
<td>1836</td>
<td>5.856</td>
<td>-1.8147</td>
<td>0.8967</td>
</tr>
<tr>
<td>13137</td>
<td>5.5521</td>
<td>-1.3155</td>
<td>2.9342</td>
</tr>
<tr>
<td>7054</td>
<td>5.433</td>
<td>-14.1886</td>
<td>0.0086</td>
</tr>
<tr>
<td>21356</td>
<td>5.394</td>
<td>-1.125</td>
<td>3.3838</td>
</tr>
<tr>
<td>2102</td>
<td>5.2989</td>
<td>-1.0127</td>
<td>2.406</td>
</tr>
<tr>
<td>5722</td>
<td>5.2721</td>
<td>-1.3506</td>
<td>0.0001</td>
</tr>
<tr>
<td>12767</td>
<td>5.265</td>
<td>-1.3465</td>
<td>2.1881</td>
</tr>
<tr>
<td>16525</td>
<td>5.1705</td>
<td>-14.9457</td>
<td>0.1384</td>
</tr>
<tr>
<td>1837</td>
<td>5.0351</td>
<td>-2.6299</td>
<td>1.1922</td>
</tr>
</tbody>
</table>

**D. Top Scoring Compounds**

As evident from the virtual screening, the pharmacophore was carried out resulting in a hit list of 421 compounds, and the docking studies showed that 24 compounds with high docking scores have good binding capacity with histamine H1-receptor. Parts of the compounds have been reported to have the pharmacological activity related to H1 receptor inhibition by literatures. Lin found that Baicalin (ID 2106) extracted from *Scutellaria rivularis* have the anti-inflammatory activity against carrageenan-induced paw edema in rats [22]. Cortisone (ID 6853) and cuscohygrine (ID 1836) were discovered to have the active of anti-allergy [23], [24]. Matsuda found that Batatasin III (ID 2165), 2′,6′-Bis-3,3′-dihydroxy-5-methoxybibenzyl (ID 2456), Gymconopin A (ID 9099) and Gymconopin B (ID 9100) extracted from the tubers of *Gymnadenia conopsea* had an antiallergic effect on ear passive cutaneous anaphylaxis reactions in mice [25]. To a certain extent, the calculation and screening results may provide an explanation for the pharmacological effects of the plant herbs. However, the results need further experiments to confirm.

**IV. CONCLUSIONS AND FUTURE WORK**

In this paper, the computational method based on pharmacophore, molecular docking and virtual screening was established to quest for H1 receptor antagonists from Traditional Chinese herbs. The pharmacophore model established was used to identify the common features of H1 receptor antagonists from known active compounds. And molecular docking was employed to study the detailed binding mode between the ligand and active site of H1 receptor. The computational approaches showed the advantage in saving time and resources. It’s feasible to quest for H1 receptor antagonists from Traditional Chinese herbs by using virtual screening based on pharmacophore and molecular docking. Several active compounds were identified from the structurally diverse mixture in traditional Chinese medicine. Thus, it revealed an available tool to quest for H1 receptor antagonists by virtual screening. It can also be used in other targets, not limited to H1 receptor. In the following study, the compounds hit by pharmacophore model and molecular docking need further verification using related biological experiments, this will help to find effective H1 receptor antagonists and lead compounds from Traditional Chinese medicine.

**ACKNOWLEDGEMENT**

This work was financially supported by the Foundation of National Natural Science Foundation of China (No. 81173522) and National Key Technology R&D Program (No. 2008BA151B01) in Beijing University of Chinese Medicine.

**REFERENCES**


Xing Wang was born in Henan Province, China in 1983. He graduated from the College of Pharmacy in Henan University of Traditional Chinese Medicine and gained Master's degree in 2009. His major field of study is the TCM information Engineering. He is now working on his PhD in Beijing University of Chinese Medicine focusing on "Active Compounds and Mechanism of action Discovery in TCM". During the school period, he has published seven research papers and won the National Scholarship. The partly published articles include: Rational questing for Inhibitors of ECE-1 from *Salvia miltiorrhiza* by combining ligand and structure based virtual screening, Rapid analysis of *Fructus Forsythiae* by near-infrared spectroscopy, Application of pharmacophore technique in the study of TCM.

Yuhong Xiang was born in Hebei Province, China, in 1976. She graduated from the University of Science and Technology of China and gained Ph.D in 2005. Her major field of study is analytical chemistry. She is now an associate professor in capital normal University. Her research mainly focuses on the computer aided drug design. More than 30 scientific papers have been published. The partly published articles include: Pharmacophore and QSAR studies to design novel histone deacetylase 2 inhibitors. A novel two-step QSAR modeling work flow to predict selectivity and activity of HDAC inhibitors.

Zhenzhen Ren was born in Hebei Province, China, in 1985. Zhenzhen Ren graduated from the Chengde Medical College and gained Bachelor of Science degree in 2011. Now she is studying at the Traditional Chinese Medicine College in Beijing University of Chinese Medicine for the Master's degree. Her major field of study is TCM design and optimization. She is now a master degree candidate in Beijing University of Chinese Medicine and she has won the scholarship of school. Her scientific research directions is biological network-based design and optimization of Traditional Chinese Medicine. As a participant she has published articles include: Pharmacophore Model Generation of thrombin Inhibitors, Rational questing for Inhibitors of ECE-1 from *Salvia miltiorrhiza* by combining ligand and structure based virtual screening.