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Potential synergism and inhibitors to multiple target enzymes of Xuefu Zhuyu Decoction in cardiac disease therapeutics: A computational approach

Qin Huang, Xuebin Qiao and Xiaojie Xu*

Peking University, Colloge Chemistry & Molecular Engineering, Beijing 100871, PR China

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Abstract—In order to study the drug-like features of Xuefu Zhuyu Decoction (XFZYD), a Traditional Chinese Medicinal recipe, three different computational methods were introduced to characterize the molecules in XFZYD, including chemical space distribution, docking protocol, and ADME prediction. Chemical space compared between the compound sets from XFZYD and drug/drug-like shows XFZYD may have desired interaction with broader protein targets. And the docking results show that the XFZYD is a broad-spectrum recipe inhibiting many important target enzymes. Together with the predictions of ADME properties, clue of potential synergism of XFZYD was obtained.

Natural products have been the main sources of drugs for quite a long time. According to the literature, more than 25% of the marketed drugs are coming from natural products nowadays.[1] Medicinal information accumulated from traditional medicine can provide valuable clues for finding new drugs in natural products. TCHs, the rich natural resources in China, have been developed for therapeutic use for more than thousands years[2] and a great amount of recipes have been preserved until now.

Current research and development in TCHs are usually focused on extraction, isolation, and analysis the active components in original plants of TCHs that have achieved some important success. It is a practical method to find the effect of single compound. However, Traditional Chinese Medicinal (TCM) recipe is based on compatibility of prescriptions[3] which related to synergism mechanism due to its complex components. Thus, in this report, we try to find hints of synergism in TCM based on well-known chemoinformatics method,[4–6] hoping to get a general method to assist modern TCM development.

We chose a system consisting of compounds in original plants of XFZYD, a recipe developed by Wang Q. R. in Tsing Dynasty[7] which was widely used in cardiac system disease[8–10] and is a broad-spectrum recipe like other TCM recipes. We mainly studied the molecular diversity properties, the ADME/Tox properties, and the interactions between molecules and target enzymes of XFZYD to illustrate the potential synergism in XFZYD. Five hundred and one compounds identified in XFZYD's original plants were collected from Chinese Herbal Drug Database[11] developed by our laboratory and other literature.[12,13] All molecular structures were optimized by molecular mechanics optimization method under MMFF force field, and the stop condition was set as the RMS of potential energy smaller than 0.001 kcal $Å^{-1}$ mol^{-1}. For those flexible compounds, the most stable conformations were chosen from standard conformational analysis. The whole work was conducted using commercial software Cerius2.[14] To describe the complete features of XFZYD, none of pre-screening filters were plugged in, for example, Lipinski's Rule of Five[15] or ADME/Tox properties.

Chemical space[16] is a generalized data visualization method to describe the well-known beliefs among chemists that similar compounds may have similar properties. It is defined by calculating given set of descriptors for each molecule and using these values as coordinates in the multidimensional space. The characteristics of

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* Corresponding author. E-mail: xiaojxu@pku.edu.cn

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points distribution denote the similarities and differences among given sets of molecules. Here, 34 common descriptors were used to define a chemical space for compounds in XFZYD. Its property profiles were compared with a drug/drug-like compounds set collected from Aardiovascular Ascular Pharmacology[17] in the same chemical space. Results of some descriptors are shown in Table 1 and Figure 1–8.

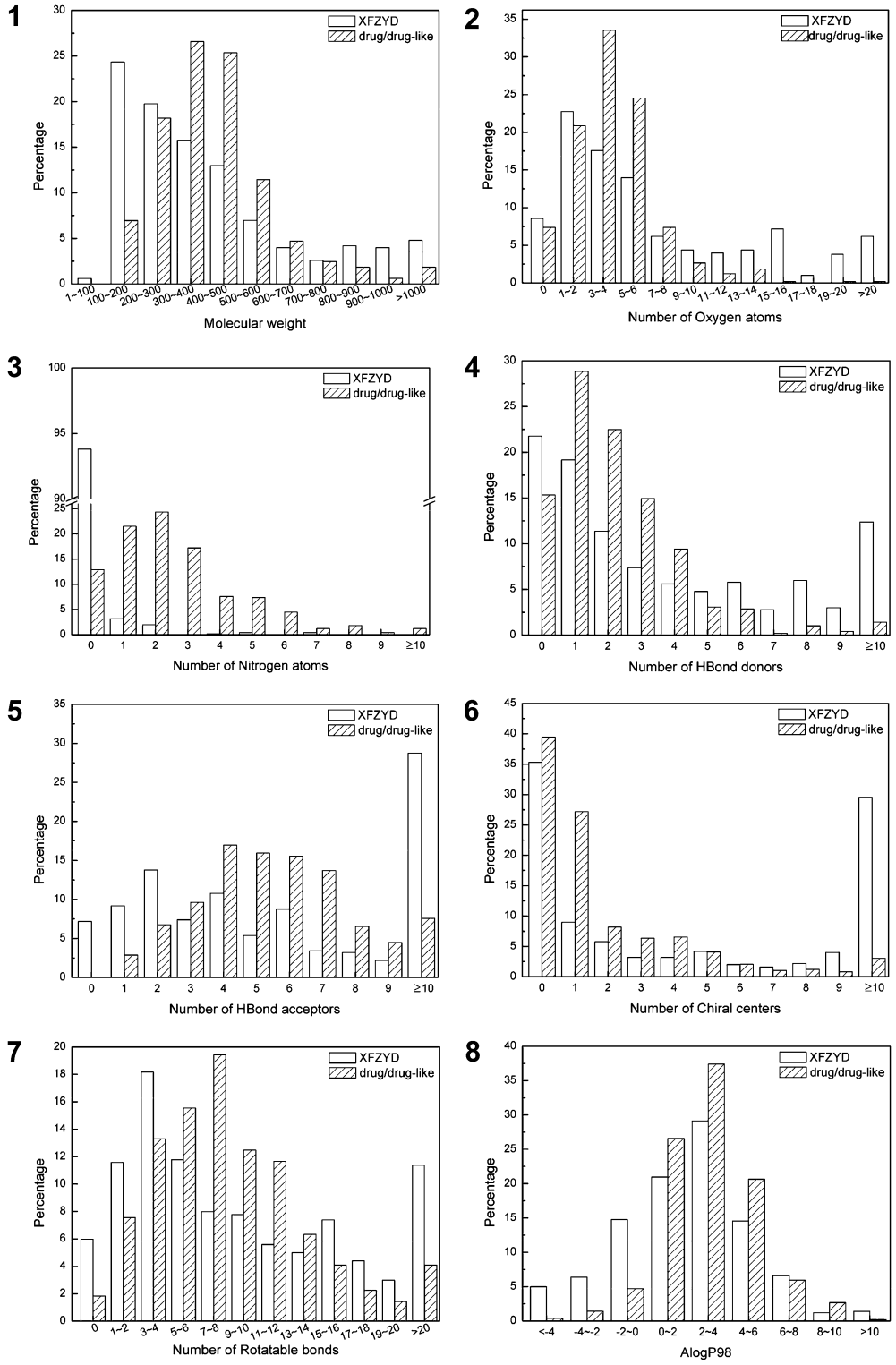
From the results, it is obvious that the mean values of molecular weight (MW) of compounds in XFZYD are close to those of the drug/drug-like molecules. However, the median values of MW of drug/drug-like molecules are greater than that of XFZYD. In the MW distribution chart, though more molecules fall in the interval 0–100, the MW of compounds in XFZYD reaches peak at interval 100–200, then decreases step by step, but has a higher tail after 800 that makes the mean value of XFZYD close to that of drug/drug-like molecules. The peak of drug/drug-like molecules' MW is 300–400. But its distribution is narrower. Most compounds in XFZYD are up to Lipinski's Rule of Five. When considering the compounds which have MW greater than 800, most of them have one or more glucose ring which makes the compounds hard to be absorbed or metabolized before they enter human digestive system. The most obvious difference between XFZYD and drug/drug-like molecules exists in the number of oxygen atoms, nitrogen atoms, and other heavy atoms. The shape of distribution of number of oxygen atoms is like that of hydrogen donors. The number of hydrogen donors and acceptors is related to the affinity with target enzymes. Molecular flexibility is another important property. Klebe et al.[18] have shown that if a flexible and a rigid ligand can form the same pattern of hydrogen bonds and hydrophobic interactions with protein, the rigid ligand will exhibit stronger binding due to lower entropic losses. The distribution of number of rotatable bonds is shown in Figure 7. More than 10% compounds in XFZYD have more than 20 rotatable bonds. Some of these compounds are long chain alcohols and carboxylic acids which hardly have therapeutic effect. Number of rings of XFZYD is more than those of drug/drug-like molecules. It is well known that lipophilicity plays a very important role in the ADME/Tox properties. *A*log *P*98 was also calculated to help learning lipophilicity. *A*log *P*98 value of most compounds in XFZYD is lower than 5, and the shape of distribution of *A*log *P*98 of XFZYD is similar to that of drug/drug-like molecules. Some results were in accordance with observations of Feler et al.[19] to some degree. But as what we study is a selected case, our results had some differences, for example, the number of nitrogen atoms.

In order to perceive reasonable and intuitionistic information from multiple descriptor values, principal component analysis (PCA) was performed to map these multiple descriptor values into a 2D plane (Figs. 9 and 10). Results show the structural properties of molecules in XFZYD are more diverse than those of the drug/drug-like molecules. TCM recipe system can be seen as natural combinatorial chemical libraries. It is an indication that the molecules in XFZYD may have desired interaction with broader protein targets than the drugs/drug-like molecules.

Docking protocol was used to prove the desired interaction. To highlight the compounds in XFZTD which are most likely active in cardiovascular disease system, docking protocol was performed to show the interaction with common cardiovascular target enzymes using LigandFit (in Cerius2). Because Renin-Angiotensin System (RAS) was the main humoral system modulating the cardiovascular physiological function, rennin, ACE, and ACE2 were mainly concerned. We used the Ligandscore of the original protein complex as the cutoff value in this protocol. Results are shown in Table 2 in which we can see many molecules have good interaction with the proteins. Other target enzymes involved in cardiac disease (results in Table 2) were tested too. The total number of compounds with good result is 283. And among them, there are 100 compounds of which each

Table 1. Maximum/minimum and median/mean values of some different properties between compounds in Xuefu Zhuyu Decoction original plants and drug/drug-like molecules

	XFZYTD (contains 501 compounds)				Drug/drug-like (contains 489 compounds)			
	Max	Min	Median	Mean	Max	Min	Median	Mean
Molecular weight	1549.62	59.11	352	416.3	2180.31	116.12	390.52	417.45
No. of carbon atoms	69	3	19	21.93	98	3	20	21.56
No. of oxygen atoms	38	0	5	7.45	33	0	4	4.14
No. of nitrogen atoms	7	0	0	0.13	24	0	2	2.60
No. of heavy atoms	107	4	25	29.52	155	8	28	29.14
No. of rings	12	0	3	3.32	9	0	2	2.68
No. of rotatable bonds	57	0	7	9.9	93	0	8	8.79
No. of hydrogen acceptors	38	0	5	7.5	35	1	5	5.74
No. of hydrogen donors	23	0	2	4.1	31	0	2	2.26
Molecular volume	1351.25	74.44	319.47	385.11	1950.57	106.94	361.45	379.88
Molecular surface area	1589.77	112.42	403.52	476.77	2473.97	140.41	456.96	480.84
Total polar surface area	863.78	0	161.96	214.07	955.55	0	170.70	177.26
Total hydrophobic surface area	1506.48	66.95	386.15	435.15	1356.33	0	452.97	423.18
*A*log *P*98	18.41	−9.55	2.2	1.96	10.96	−7.58	3.02	3.00
No. of chiral centers	41	0	3	6.61	27	0	1	2.1
Molecular flexibility index	45.79	0.86	5.36	7.266	53.36	1.18	6.39	7.05



Figures 1–8. Each figure is a property distribution plot between compounds in XFZYD, and drug/drug-like molecules set, including MW, number of oxygen, number of nitrogen, number of hydrogen bond donors, number of hydrogen bond acceptors, number of chiral centers, number of rotatable bonds, and *A*log*P*98.

compound has computational interaction with more than one target enzymes, and some compounds, such as manninotriose have interaction with three different target enzymes. The idea that promiscuous drugs might be more effective than targeted ones has also been emerging from efforts to understand how antipsychotic drugs work and cardiovascular disease tends to result from multiple molecular abnormalities, not from a single defect,[20] this result will help to explain why XFZYD has good effect in curing cardiovascular disease.

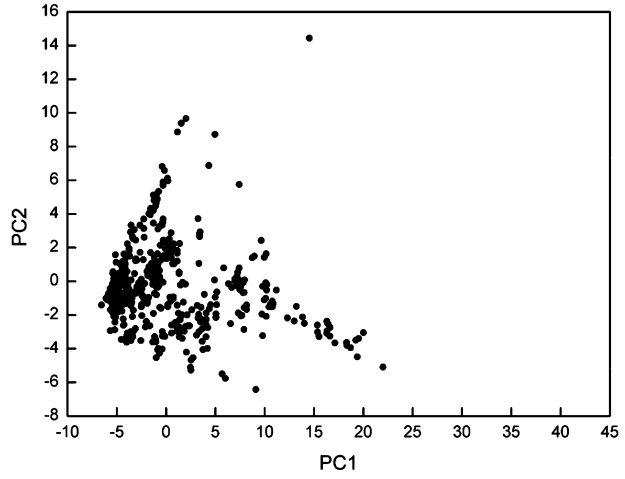


Figure 9. The plot of the first two principal components of compounds in XFZYD.

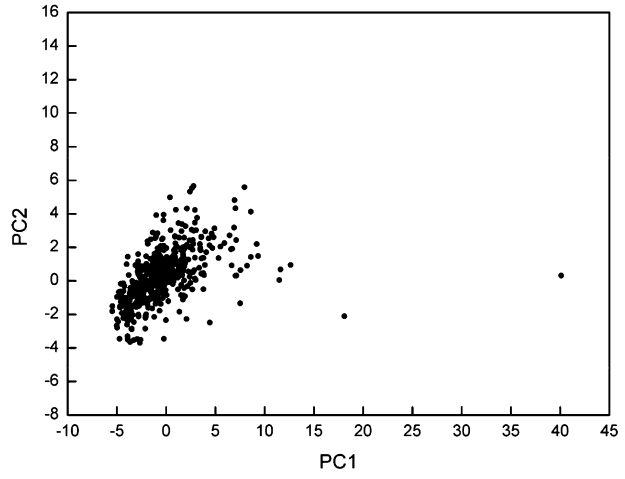


Figure 10. The plot of the first two principal components of drug/drug-like molecules.

As the XFZYD was initially an oral decoction, ADME/Tox properties of the compounds in XFZYD were predicted. Results are shown in Figure 11.

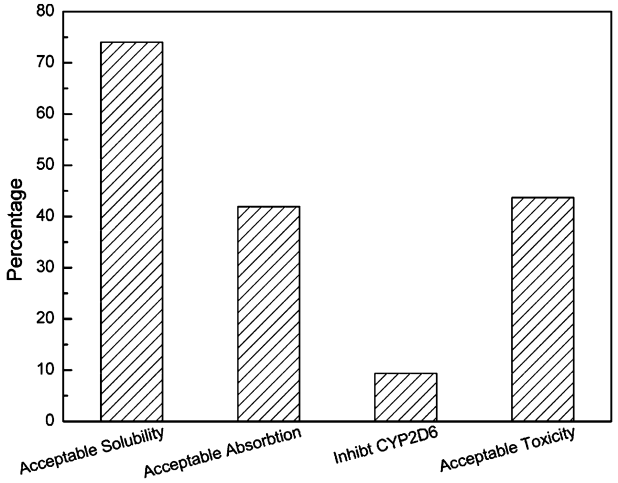


Figure 11. The plot of acceptable ADME/Tox properties of compounds in XFZYD. Acceptable solubility means aqueous solubility level value in the interval from −6 to 0, which is drug-likeness possible; acceptable absorption means human intestinal absorption level is 0 (good absorption) or 1 (moderate absorption); Inhibit CYP2D6 means likely to inhibit CYP2D6 enzyme; and acceptable toxicity means unlikely to cause dose-dependent liver injuries.

Good docking results (Table 2) show that XFZYD is a broad-spectrum recipe. It has abundant drug-like and lead-like compounds as potential inhibitors for multiple targets with multiple pathways of cardiac disease. However, the literature did not prove most compounds having high activity or those active compounds are very low in original plants. Figure 11 shows the ADME/Tox properties of compounds in XFZYD. Of course, the prediction of ADME is not very reliable, especially the hepatotoxicity and P450 2D6 enzyme inhibition properties. We just use these predicted results as reference here. More than 70% compounds have acceptable aqueous solubility. And as to blood brain barrier, near half of compounds have not bad value. But the human intestinal absorption, hepatotoxicity, and cytochrome P450 2D6 enzyme inhibition properties are not as good as expected, especially more than half of compounds have bad hepatotoxicity property. We considered these

Table 2. Number of hits with multi-target enzymes of the compounds contained in XFZYD original plants[a] (use the Ligandscore of original ligand with the protein as cutoff value)

Plants	No. of Compound	Renin	ACE	ACE2	VGFR	HMG-CoA, site1	HMG-CoA, site2	Pgp, ATPsite	Pgp, ADPsite
Total	501	10	128	None	183[b]	64	34	10	13
Achyranthes bidentata	14	—	3	—	2	—	—	—	—
Angelica sinensis	77	—	11	—	55	—	—	—	—
Bupleurum chinensis	74	1	3	—	30	—	1	—	1
Carthamus tinctoria L.	24	—	7	—	5	4	3	3	2
Citrus aurantii	23	3	2	—	10	1	4	1	—
Glycyrrhiza uralensis	104	3	35	—	4	25	14	1	7
Ligusticum wallichii	78	—	23	—	47	3	1	—	—
Paeonia rubra	19	1	8	—	4	7	7	2	1
Platycodon grandiflorum	30	—	1	—		—	—	—	—
Prunus persica	6	—	6	—	3	4	—	—	—
Rehmannia glutinosa	82	1	33	—	34	20	4	3	2

[a] The codes of PDB used as the targets for docking were: Renin(1BIL), ACE(1J37), ACE2(1R42), HMG-CoA(1HW8), Pgp (1MV5).
[b] Some compounds are contained in different plants at the same time. For more details, see the supplement manuscript.

questions involved in secondary metabolites in human body and how compounds assist other compounds to enter human body and act on protein conformation change to accept the fit molecules. These questions lead to synergies in TCHs systems. Medicinal chemists have investigated the potential synergism of natural products in some therapeutic field.[21] Keung et al. have shown that the EC_{50} of the graded dose–response of extract daidzin is ten times as that of pure daidzin.[22] P-glycoprotein (Pgp), one of the multi-drug resistance proteins, can facilitate oral drug uptake and benefit drug–drug pharmacokinetic interaction. Drugs that inhibit Pgp will increase the oral bioavailability to achieve therapeutically relevant drug concentrations in plasma.[23] Docking protocol was also performed with Pgp (see Table 2). Results give an interpretation of potential impact on improving ADME/Tox properties of XFZYD in plasma.

In conclusion, we describe property distribution, ADME/Tox properties, and docking results of XFZYD. The computational results show that XFZYD has better structural diversity compared to the selected drug/drug-like molecules, and has abundant drug-like and lead-like compounds as potential inhibitors for multiple targets. With ADME/Tox prediction, the whole results give clues that multiple pathways and potential synergism exist in curative mechanism of TCM recipe.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.bmcl.2006.12.078.

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