Virtual Evaluation on the Activities of Phthalides and Terpenoids from *Angelica sinensis*

PEI Yuan[1,2], TAN Chu-bing[1], XU Wei-ren[1*], LIU Peng[1], LIU Bing-ni[1], LIU Wei[1], CHEN Cheng-lung[3], TANG Li-da[1]

1. Tianjin Key Laboratory of Molecular Design and Drug Discovery, Tianjin Institute of Pharmaceutical Research, Tianjin 300193, China
2. Basic Medical College, Tianjin Medical University, Tianjin 300070, China
3. Department of Chemistry, National Sun Yat-sen University, Kaohsiung 80424, China

Abstract: **Objective** To elucidate potential activities of phthalides and terpenoids from *Angelica sinensis* by theoretical docking calculation. **Methods** Eleven components of phthalides and terpenoids were selected as ligand. The crystalline structures of targets related to common diseases were used as the receptors for calculation. The calculations were conducted with Schrödinger software package. The grading standard of selectivity was developed according to *G*-score between ligands and receptors. **Results** Selective targets of phthalides and terpenoids were related to nevous system diseases, cancer, pain, diabetes, cardiovascular disease, liver cirrhosis, nephrotic syndrome, inflammatory diseases, rheumatoid arthritis, dermatosis, leukemia, microbial inflections, immune diseases, and hypercholesterolemia. In addition to the medical treatments reported in the literature, our research also indicated that these two classes of compounds may be used for tumor, diabetes, rheumatoid arthritis, dermatosis, leukemia, liver cirrhosis, and nephrotic syndrome. According to our research, the effects of phthalides and terpenoids may be not so strong. **Conclusion** The effects of phthalides and terpenoids on diseases founded through virtual evaluation accord greatly with those reported in experiment and clinic. The combination of computer-aided drug evaluation technique and experiment is definitely an important and fast way to investigate the effects and mechanisms of traditional Chinese medicine.

Key words: *Angelica sinensis*; phthalides; terpenoids; virtual evaluation
DOI: 10.3969/j.issn.1674-6384.2010.03.012

Introduction

Angelica sinensis (Oliv.) Diel is one of the most commonly used traditional Chinese medicines. It has been applied for the treatment of many blood-related diseases. The current research is focusing on the particular component, volatile oil, in *A. sinensis*. Although there is only 0.62% volatile oil in the total contents in *A. sinensis*, it is found that this species have enriched chemical components and have a lot of applications in clinical medical treatment (Ni *et al*, 2007). Evidence shows that volatile oil can smooth muscle of uterus, reduce blood pressure, improve myocardial ischemia, anti-cardiac dysrhythmias, relive asthma, inhibit nervus system, promote body anti-inflammation, and relieve pain (Du *et al*, 2005; Wei *et al*, 2009; Pei *et al*, 2010; Lan *et al*, 2009). However, due to the multi-component complication of Chinese drug, it is difficult to understand the detailed mechanism of the function of the drug by experiment method. Using computer aided virtual screening technique to investigate action mechanism of Chinese drug can significantly reduce human and material resources for experiment study. Molecular docking based on three-dimensional structure of receptor molecules is an important way to find leading compounds, and is one of the most important methods of computer-aided drug design. Molecular docking provides more intuitive and clear description of the action mechanism and it is possible

* Corresponding author: Xu WR Tel: +86-22-2300 6862 E-mail: xuwr@tjipr.com
Author: Pei Y, female, Henan Province, Graduate student E-mail: peiyuan2007@yahoo.com.cn
Received: December 16, 2009; Revised: April 22, 2010; Accepted: June 29, 2010
Support: Supported by the Ministry of Science and Technology of the P. R. China (No. 2007BAI41B01)

to study the interaction between drug and target enzyme (Zeng *et al*, 2007).

The current research proposes a theoretical method to evaluate the effectiveness of the drug to specific diseases. The chosen ligands are compounds of phthalides and terpenoids, which are components of volatile oil in *A. sinensis* (Zhou, Xie, and Yan, 2004). Given in Fig. 1 and Fig. 2 are the structures of these eleven chosen compounds.

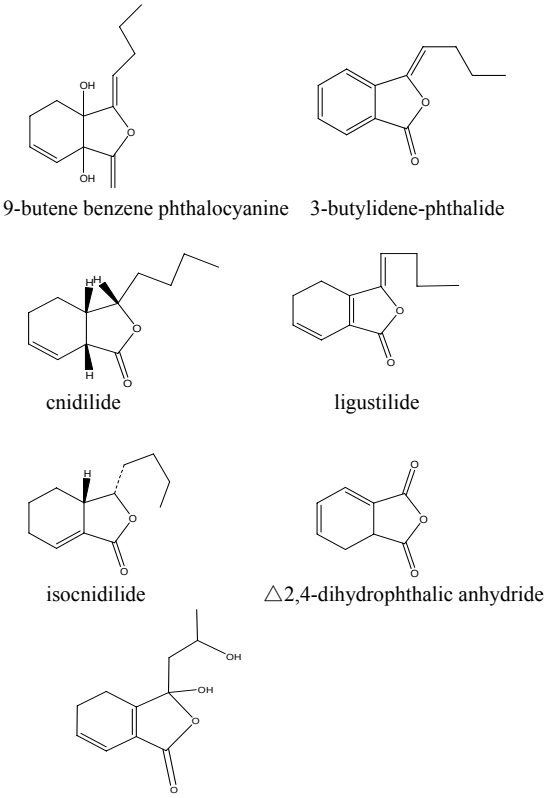

Fig. 1 Structures of phthalides

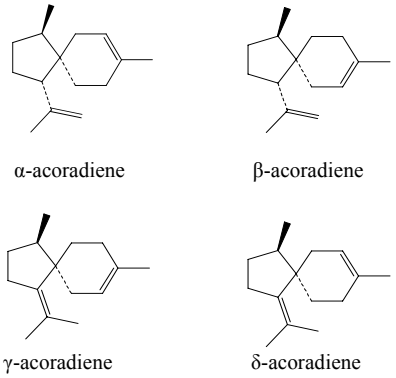

Fig. 2 Structures of terpenoids

Methods

All structures in Fig. 1 and Fig. 2 were optimized with OPLS_2005 force field (Friesner *et al*, 2004). The atomic partial charge located at different atoms was then obtained with this force field based on the optimized structure. All calculations were performed by software Schrödinger 2008. The target proteins were selected from Therapeutic and Target Database in Bioinformatics and Drug Design group (BIDD) (http//xin.cz3.nus.edu.sq/). The three-dimensional crystalline structures of these proteins were adopted from the protein database PDB (http://www.rcsb.Org/pdb/) (Deng *et al*, 2005). Given in Table 1 are these selected target proteins. In the table, the proteins are grouped into different classes according to their biological functions.

To investigate the interaction between the drugs (donor) and target proteins (receptor), the selected proteins were pretreated by removing all waters, unimportant ions, and other subunits. The pretreated proteins from PDB database were then saturated by adding hydrogen atoms (Joy *et al*, 2006). This was carried out by modules Protein Preparation Wizard in Schrödinger software. The interaction between donor drug and receptor protein was investigated by usual docking method. In the docking method, the structure of protein was fixed and drug was placed in the active zone of protein (Li, Zheng, and Wang, 2006). The drug molecule was allowed to move, rotate, and change internal configuration to some position which reaches the minimum of interaction energy surface (Friesner *et al*, 2004). The possible effectiveness of drug to protein interaction was evaluated by assigning *G*-score provided by Glide module in Schrödinger software. The more negative the score, the better the effectiveness of drug interacts with protein. In our virtual evaluation, the drug-to-protein interaction was assigned as specific and non-specific interaction. The specific interaction is the interaction between specific drugs (which have been proved effective by experimental method) to specific protein. The non-specific interactions are the interactions between randomly selected drugs to protein. Logically, the score for the specific interaction between drug and protein should be higher than non-specific interaction. The *G*-score of non-specific interaction can be related to molecular properties of drug.

Using QSAR method, the molecular descriptors (chilv_C, PEOE_VSA-5, SlogP_VSA3, SlogP_VSA5)

Table 1 Selected proteins and their PDB codes of different targets

Target proteins	PDB code
G protein-coupled receptor	1ff4, 1ilq, 1iss, 1rso, 2e4y, 2e4z, 2hlb, 2rh1
tyrosine kinase receptor	1agw, 1h9o, 1i44, 1j91, 1n8y, 1oec, 1pjk, 1pkg, 1qsz, 1rw8, 1syo, 1xkk, 2itn, 2oj9, 2p2h, 2rfn
ion channel receptor	1jvm, 1kl8, 1mqg, 1mqh, 1pb7, 1vso, 2br7, 2f3z, 2f34
cytokine receptor	1alu, 1h1b, 1he7, 1ilp, 1ira, 1rwk, 1usm, 2erj, 3bpn
nuclear receptor	1ere, 1m2z, 1sox, 1yje, 1ytv, 1yy4, 2aa5, 2pjl, 3erd
oxido-reductase	1b1c, 1dq8, 1egy, 1gt8, 1js3, 1lrt, 1og5, 1oj9, 1pq2, 1qyx, 1t4o, 1tv5, 1z11, 2b6, 2f9q, 2hi4, 2q7m, 2vom, 2z5y
kinase	1a9u, 1b38, 1ckp, 1e2d, 1gxd, 1it6, 1mp8, 1oi9, 1pmn, 1pmq, 1roe, 1s9i, 1s9j, 1tvo, 2b9f, 2baq, 2eva, 2f15, 2gmx, 2g01, 2gtm, 2h6d, 2peo, 2uv4, 3cc6
transferase	1cjw, 1ezf, 1iic, 1rxy, 1sto, 1uou, 1z8d, 2jgy, 2nzt, 2oio, 2yhx, 3b8al
hydrolase	1bzc, 1c25, 1d4h, 1dx4, 1dx6, 1f6w, 1gfw, 1gjc, 1gmy, 1hii, 1j1a, 1kn6, 1mx9, 1n16, 1npz, 1poq, 1r4l, 1ro6, 1so2, 1taz, 1xom, 1ym9, 1zd5, 1zll, 2gdd, 2hbg, 2hd1, 2jg4, 2nqd, 2oc2, 2oud, 2oun, 2qly, 2qyk, 2qym
synthetase	1cqe, 1cx2, 1fe2, 1hvy, 1t4e, 1w6k, 1yq7, 2cg5, 1m9j
other enzymes	1a4g, 1a7t, 1bgj, 1bmc, 1cao, 1cjk, 1d3d, 1dtq, 1f8a, 1gl9, 1ing, 1kop, 1ohw, 1p9d, 1pko, 1qz9, 1s16, 1tr4, 1twa, 1y5m, 1ykd, 1z5a, 1zxm, 2b8v, 2col, 2fjt, 2hk2, 2hu4, 2o5c, 2o95, 2ovx, 2v5w
functional proteins	1aap, 1kdx, 1mf8, 1owt, 1qmf, 1u3b, 1uhn, 1xox, 1yfq, 1z6f, 2c5w, 2cbz, 2fk3, 2i3i, 2idh, 2j9p, 2uvl, 2uwy, 1bz4, 1cxv, 1fk6, 1ijq, 1jv2, 1moy, 1mqb, 1t1l, 1tou, 1ypu, 1z1l, 2ast, 2fcw, 2fyl, 2hen, 2iqc, 2qo9, 1yf4, 1yos, 1z3s, 2bbr, 2cjs, 2cjt, 2dbf, 2ffu, 2fw3, 2ioi, 2j7x, 2jcr, 2nmn, 2npa, 2o63, 2oci, 2p1t, 2qa6, 3bib, 3bn6, 3bqd, 3c4c, 1bfs, 1dq9, 1ejn, 1exa, 1ezq, 1fos, 1h2m, 1i7i, 1iqn, 1k3z, 1m7w, 1mr1, 1psk, 1qew, 1qz9, 1sao, 1sra, 1t5z, 1u7v, 1upv, 1xap

can be obtained for a set of non-specific drug compounds. Using linear regression analysis, we found the relation can be expressed as:

$$G\text{-score (non-specific)} = -6.323 + 0.260\ \text{chilv\_C} - 0.013\ \text{PEOE\_VSA-5} - 0.009\ \text{SlogP\_VSA3} + 0.007\ \text{SlogP\_VSA5} \quad (1)$$

To evaluate effectiveness of a drug to protein, we calculate the difference of G-score:

$$\Delta G = G\text{-score} - G\text{-score (non-specific)}$$

Where *G*-score was obtained form Glide docking and *G*-score (non-specific) was obtained by equation (1) form molecular properties. According to the previous experience (Xing *et al*, 2009), strong selective drugs have $\Delta G < -4.5$ and labeled by "+++"; moderate selective drugs have $-4.5 < \Delta G < -3.0$ and labeled by "++"; non-selective drugs have $-3.0 < \Delta G < -1.5$ and labeled by "+", respectively. Using this ΔG evaluation method, we can determine the selectivity of drugs to specific proteins.

Results and discussion

The calculated nonspecific *G*-scores of selected phthalide-class compounds are: –5.45, –5.32, –5.17, –5.19, –5.08, –4.09, –5.27, and –1.15. For selected terpenoid-class compounds, the non-specific *G*-scores are –4.62, –4.62, –4.60, and –4.60, respectively. The calculated ΔG and the selectivity assignments of these compounds are listed in Tables 2 and 3. Target proteins and their related diseases are listed in Table 4.

The results in Table 2 show that the main possible targets of phthalide class are oxido-reductase, hydrolase, kinase, and functional protein; Other targets are ion channel receptor, synthetase, tyrosine kinase receptor, nuclear receptor, and transferase. Since their grading evaluation results are "+", the interaction may be not so strong. These targets related diseases are noninsulin-dependent diabetes mellitus, autoimmune diseases, leukemia, microbial inflections, parasitic diseases, nervous system diseases, cardiovascular disease, respiratory diseases, rheumatoid arthritis, dermatosis, and cancer. Reported in the literature, phthalides can treat nervous system diseases (Wu and Luo, 2006), antiasthmatic, slow down the heart rate and antiarrhymic, enhance immunity, anti-inflamatory, and analgesic (Ni *et al*, 2007). We can see that the docking result is consistent with the reported literature.

In Table 3, the results show that the possible targets of terpenoids are transferase, hydrolase, synthetase, oxido-reductase, kinase, ion channel receptor, nuclear receptor, and functional protein. Their grading evaluation

Table 2 Grading evaluation of interaction between phthalides and targets

Component	+
8,11-dihydroxy ligustilide	kinase: 2gmx, 1pmq oxido-reductase: 2z5y, 1oj9 hydrolase: 1dx6, 1p0q, 1dx4 functional protein: 3c4c, 2jcr;
9-butene benzene phthalocyanine	ionchannel receptor: 2br7, 1kl8 oxido-reductase: 1t4o, 2z5y, 1oj9; hydrolase: 1mx9, 1dx6, 1dx4, 1poq, 1ro6, 1so2, 1taz, 1xom, 1z11, 2hd1, 2oun2qyk, 2qym functional protein: 1g73, 2cjs2cjt, 2ffu 2oci 3bib, 2cbz
3-butylidenephthalide	synthetase: 1cqe oxido-reductase: 1cx2, 1og5, 1pq2, 2f9q, 2hi4, 2uom, 1z11, 2b6, 1egy, 1b1c tyrosine kinase receptor: 1rw8 functional protein: 3c4c, 2p1t, 1exa, 1xap, 1g73, 2cjs, 2cjt, 2ffu, 2oci, 3bib
acnidilide	oxido-reductase: 1cx2, 2z5y, 1oj9 kinase: 2gmx, 1pmq hydrolase: 1mx9, 1dx6, 1p0q, 1dx4 functional protein: 2p1t, 1xap, 1exa, 1g73 2cjs 2cjt, 2ffu 2oci 3bib other enzyme: 1y5m
△2,4-dihydriphthalic	hydrolase: 1mx9
ligustilide	oxido-reductase: 1cx2, 1og5, 1pq2, 2f9q, 2hi4, 2uom, 1z11, 2b6, 1b1c, 1egy kinase: 2gmx, 1pmq hydrolase: 1dx6, 1p0q, 1dx4 functional protein: 1g73, 2cjs, 2cjt, 2ffu2oci, 3bib
isocnidilide	oxido-reductase: 1cx2, 1og5, 1pq2, 2f9q, 2hi4, 2uom, 1z11, 2b6, 1egy, 1b1c kinase: 2gmx, 1pmq synthetase: 1cqe hydrolase: 1dx6, 1p0q, 1dx4 other enzyme: 1y5m functional protein: 1g73, 2cjs, 2cjt, 2ffu 2oci 3bib

Table 3 Grading evaluation of interaction between terpenoids and targets

Component	+
α-acoradiene	transferase: 1ezf hydrolase: 1mx9 synthetase: 1w6k functional protein: 1fk6, 2p1t, 1xap, 1exa, 1upv, 2qa6, 2j7x, 3bqd, 1t5z ionchannel receptor: 2br7, 1kl8 nuclear receptor: 1sox, 1yy4, 1ere, 2aa5, 3erd
β- acoradiene	transferase: 1ezf, 2oio synthetase: 1w6k, 1fk6 hydrolase: 1mx9,1dx6,1p0q,1dx4 ionchannel receptor: 2br7,1kl8 nuclear receptor: 1sox, 3erd,1yy4,1ere, 2aa5,1m2z functional protein: 2p1t,1xap,1exa,1upv,2qa6,2j7x,3bqd,1t5z, 1usm, 1m7w
γ- acoradiene	oxido-reductase: 2f9q, 2hi4, 2uom, 1z11, 2b6, 1egy, 1b1c, 1pq2, 1og5 synthetase: 1w6k kinase: 2b9f, 2eva, 1a9u, 2baq, 2g01, 2gtm, 1tvo, 1pmn, 1s9j, 2gmx, 1pmq transferase: 1ezf, 2oio nuclear receptor: 1sox, 3erd, 1yy4, 1ere, 1m2z, 2aa5 hydrolase: 1mx9, 1dx6, 1p0q, 1dx4, 1ro6, 1so2, 1taz, 1xom, 1z1l, 2hd1, 2oun, 2qyk, 2qym functional protein: 1zll, 1fk6, 3c4c, 2p1t, 1xap,2p1t, 1xap,1exa, 1upv, 2qa6, 2j7x, 3bqd,1t5z, 1m7w, 1usm
δ- acoradiene	oxido-reductase: 1cx2, 1og5,1pq2, 2f9q, 2hi4, 2b6, 1egy1b1c, 2uom, 1z11 kinase: 2g01, 2baq, 2gtm, 1tvo,2b9f, 2eva, 1a9u1pmn1s9j, 2gmx, 1pmq ion channel receptor: 1jvm, 2br7, 1kl8 nuclear receptor: 1sox, 3erd, 1yy4, 1ere, 1m2z, 2aa5 hydrolase: 1mx9, 1dx6, 1p0q, 1dx4, 1ro6, 1so2, 1taz, 1xom 1z1l, 2hd1, 2oun, 2qyk,2qym functional protein: 1fk6, 3c4c,2p1t, 1xap, 1exa, 1upv, 2qa6, 2j7x, 3bqd, 1t5z, 1usm, 1m7w transferase: 1hvy synthetase: 1w6k transferase: 2oio

Table 4 Targets and related diseases

Target protein	PDB code	Related diseases
C-Jun *N*-terminal kinase	2gmx,1pmq	Alzheimer's disease, diabetes, rheumatoid arthritis, dermatosis
acetylcholinesterase	1dx6,1p0q,1dx4	Alzheimer's disease, cognitive deficits, hypoxic-ischemic encephalopathy, motor neurone disease, Parkinson's disease
CD44 antigen	2jcr	autoimmune disease, insulin-dependent diabetes mellitus, systemic sclerosis, tumors
multidrug resistance protein	2cbz	acute leukaemia, allograft rejection, autoimmune disease, depression, cancer
nicotinic acetylcholine receptor	2br7,1kl8	alcoholism, Alzheimer's disease, cancer, drug dependence, helminth, neuropsychiatric, pain, Parkinson's disease, cognitive deficits, depression
aldose reductase	1t4o	neuropathic pain, noninsulin-dependent diabetes mellitus,
carboxylesterase	1mx9	Alzheimer's disease, cardiovascular disease, hypercholestrolaemia, cocaine overdose
phosphodiesterase	1ro6,1so2,1taz,1xom.1z1l, 2hd1,2oun,2qyk,2qym	asthma, chronic obstructive pulmonary disease
mucin	2ffu 2oci 3bib	diabetes mellitus, breast cancer, immune disease, papillary thyroid carcinomas
prostaglandin G/H synthase	1cqe	cardiovascular disease, inflammatory disease
transforming growth factor receptor	1rw8	gastric cancer, liver cancer
retinoic acid receptor	2p1t,1xap,1exa	acute promyelocytic leukemia, pancreatic cancer
kDalton type IV collagenase	1y5m	atherosclerosis, neuritis, multiple sclerosis, cancer, rheumatoid arthritis
cardiac phospholamban	1zll	heart failure
low-density lipoprotein receptor	2fcw,1ijq,1ypu	Parkinson's disease
mitogen-actvated protein kinase	2baq,2g01,2gtm,1tvo,2b9f, 2eva, 1a9u 1pmn 1s9j	cancer
voltage-gated Potassium channel	1jvm	cardiac dysrhythmias
epidermal growth factor receptor	1xkk,1n8y,2itn	cancer
vasopressin receptor	1ytv	heart failure, diabetes, hypertension, liver cirrhosis, nephrotic syndrome
ROR-alpha nuclear receptor	1sox	cholestrol-related diseases, chronic inflammatory diseases
inosine-5'-monophosphate dehydrogenase	1lrt	heptatitis C, immunosuppression, leukemia, lung cancer, microbial inflections, parasitic diseases, acute respiratory; syndrome
insulin-degrading enzyme	2jg4	Alzheimer's disease
thrombin	1d3d	coronary atherosclerosis, thrombotic disease, coagulative disorders, multiple organ failure
lanosterol synthase	1w6k	hypercholesterolenia
estrogen receptor	3erd, 1yy4,1ere	brain injury, cardiovascular disease, neurodegenerative diseases, osteoporosis, breast cancer
aldosterone receptor	2aa5	heart failure, hypertension
nuclear receptor coactivator	2qa6,2j7x,3bqd,1t5z	breast cancer, prostate cancer
glucocorticoid receptor	1m2z	endocrine, inflammation, stress
hepatocyte nuclear factor	1usm, 1m7w	noninsulin-dependent diabetes mellitus
thymidylate synthase	1hvy	fungal diseases, cancer, proliferative diseases

results are also "+". Table 4 shows that these targets related diseases are nervous system diseases, cancer, pain, diabetes, cardiovascular disease, liver cirrhosis, nephrotic syndrome, inflammatory diseases, rheumatoid arthritis, dermatosis, leukemia, microbial inflections, immune diseases, and hypercholesterolemia. The results in Tables 2, 3, and 4 show that volatile oil in *A. sinensis* targets-related diseases are nervous system diseases, cancer, diabetes, cardiovascular disease, inflammatory diseases, rheumatoid arthritis, dermatosis, leukemia, microbial inflections, immune diseases, nephrotic syndrome, liver cirrhosis, and hypercholesterolemia. The docking result is also consistent with the reported literature.

In the literature, volatile oil was used as a whole part in treatment. Their activities related to decrease the

blood pressure, anti-ischemic, antiarrhymic, inhibit platelet aggregation, antiasthmatic, inhibit central nervous, enhance immunity, anti-inflamatory, and analgesic, etc. (Du *et al*, 2005). Comparing the results in Tables 2, 3, and 4, we can find that in addition to the reported pharmacological effect, phthalides and terpenoids in *A. sinensis* may be used for the medical treatment of other diseases listed in Table 4. From docking results we find new therapeutic targets and it will help treat disease.

In clinical treatment, phthalides and terpenoids belong to volatile oil and are usually used as a whole. According to our results, their targets and pharmacological effects may be different. Although the same kind of phthalide and terpenoid calss, different compounds have some different effects. It suggests that this kind of research has some advantages to reveal complicate mechanisms of traditional Chinese medicines (TCM).

A. sinensis belongs to umbelliferae class. It is a perennial herd and has properties of sweet flavor, pungent, warm in nature. As a drug, it can enrich the blood, promote blood flow, regulate menstruation, alleviate pain, and loosen bowel to relieve constipation. The volatile oil is an important source for angelica to have phamacodynamic action (Zhou *et al*, 2007). The lactone compounds are the effective components of volatile oil to have its pharmacologic actions. Since the content of TCM is very complicate, also the interactions of its components to target proteins are varied. It is difficult to carry out detailed experimental study on each component to various target proteins. Usually, only small amount of drugs can be investigated by experimental method. Therefore, the virtual evaluation with computer can help to find possible action mechanism and provide useful guide for experiment works (Zhu, Chen, and Xu, 2007).

Conclusion

In the current study, we carried out molecular docking and virtual evaluation method to investigate the possible activities of phthalides and terpenoids of volatile oil to the diseases. We found that these two classes can be used as medical treatments for many diseases. In addition to the medical treatments reported in the literature, our research also indicates that these two classes of compounds may be used for tumor, diabetes, rheumatoid arthritis, dermatosis, leukemia, liver cirrhosis, and nephrotic syndrome. According to our research, the effects of phthalides and terpenoids may be not so strong. These multi-component, multi-channel, and multi-interaction-target characters are common for TCM (Chen, 2004). Although our study provides possible medical treatment of phthalides and terpenoids of volatile oil, it needs experimental work to confirm these results. The combination of computer-aided drug evaluation technique and experiment is definitely an important and fast way to investigate the effectiveness of drugs.

References

Chen KY, 2004. Explore the mechanism of traditional Chinese medicine and safety evaluation from experimental and clinical aspects. *J Jiangxi Coll Tradit Chin Med* 16(2): 5.

Deng HW, Guo Y, Sun Y, Xu YH, 2005. Screening of new micro-molecule ligands of targetepidermal growth factor receptor. *Prog Biochem Biophys* 32(2): 180-185.

Du J R, Bai B, YU Y, Wang CY, Qian ZM, 2005. New progess of study on Angelica volatile oil. *China J Chin Mater Med* 30(18): 1400.

Friesner RA, Banks JL, Murphy RB, Halgren TA, Klicic JJ, Mainz DT, Repasky MP, Knoll EH, Shelley M, Perry JK, Shaw DE, Francis P, Shenkin PS, 2004. Glide: A new method for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy. *J Med Chem* 47(7): 1739-1749.

Joy S, Nair PS, Hariharan R, Pillai MR, 2006. Detailed comparison of the protein-ligand docking efficiencies of GOLD, a commercial package and argusLab, a licensable freeware. *Silico Biol*, 6(6): 601-605.

Lan YY, Yao XJ, Pan Q, 2009. Preparation of self-emulsifying drug delivery system of angelica oil (the wolatile oil from rhizome of *Angelica sinensis*). *Mod Pharm Clin* 24(6): 350-353.

Li SL, Zheng Y, Wang FY, 2006. Molecular docking research of new 1,5-diarylimidazoles. *J Beijing Univ Chem Technol* 33(4): 75-79.

Ni ZN, Lv GY, Lou ZH, Wu RJ, 2007. Progress of study on chemical constituent and pharmacological effect of Angelica volatile oil. *Chin J Inf Tradit Chin Med* 14(7): 93-95.

Pei Y, Tan CB, Xu WR, Liu P, Liu BN, Liu W, Han YM, Tang LD, 2010. Virtual evaluation on activities of phthalides and terpenoids from *Angelica sinensis*. *Chin Tradit Herb Drugs* 41(6): 938-941.

Wei W, Gong SX, Zhang TJ, Hu J, 2009. Research progress on composition of angelica polysacchrides and their pharmacological action. *Drug Eval Res* 32(2): 130-134.

Wu LR, Luo Y, 2006.The role of butylphthalide on the nervous system diseases and its mechanism. *Chin J Rehabil Theory Pract* 12(11): 936-938.

Xing J, Xu WR, Liu P, Liu BN, Fu HY, Liu W, Wang XL, Tang LD, 2009. Virtual evaluation on the anti-inflammatory activity of iridoids from rehmannia and cape jasmine. *Chin Tradit Herb Durgs* 40(6): 930-935.

Zeng MG, Chen LW, Zheng CS, Du J, 2007. Molecular docking method to study the effect of Fuzhengyiliu compound on cyclo-oxygenase. *Chin J New Drugs Clin Rem* 26(8): 580-585.

Zhou JJ, Xie GR, Yan XJ, 2004. *Handbook of Plant Chemical Constituents of Traditional Chinese Medicine*, Chemical Industry Press.

Zhou YH, Xie H, Wang TW, Bai HQ, 2007. Extraction and component analysis of Angelica volatile oil. *Technol Develop Chem Industry* 36(3): 33-35.

Zhu W, Chen KY, Xu SJ, 2007. Application of computerized virtual screening technique in traditional Chinese medicine. *Chin J Integr Tradit West Med* 27(3): 263-266.