Application of Reverse Docking in the Research of Small Molecule Drugs and Traditional Chinese Medicine

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Summary

With the development of structural biology and data mining, computer-aided drug design (CADD) has been playing an important role in all aspects of new drug development. Reverse docking, a method of virtual screening based on molecular docking in CADD, is widely used in drug repositioning, drug rescue, and traditional Chinese medicine (TCM) research, for it can search for macromolecular targets that can bind to a given ligand molecule. This review revealed the principle of reverse docking, summarized common target protein databases and docking procedures, and enumerated the applications of reverse docking in drug repositioning, adverse drug reactions, traditional Chinese medicine, and COVID-19 treatment. Hope our work can give some inspiration to researchers engaged in drug development.

Keywords reverse docking; drug repurposing; adverse drug reaction; Traditional Chinese Medicine; COVID-19
Introduction

Nowadays, computer-aided drug design (CADD) has been widely used in the field of medicine and has become a key step in the early stage of drug discovery and development. Compared with traditional high-throughput screening, CADD is based on the classical theory of structural biology, which greatly reduces the research cost and time and avoids blindness and limitations in the high-throughput screening process. 1) Reverse docking, as a key tool of CADD, has been sought after by the majority of pharmaceutical workers since it was proposed in 2001. 2) The idea of reverse docking can be traced back to the "Lock-key model" proposed by Fischer more than 100 years ago, 3) that is, the binding of receptor and ligand is a geometric matching process. Subsequently, Koshland 4) proposed the concept of "Induced fit" in 1958, which greatly improved the theory. The formation of the complex is the process of the mutual adaptation of the receptor and the ligand or the conformation of the receptor and the ligand will change during the binding process. Reverse docking is currently the only virtual screening method that does not require the known targets, which uses small molecule compounds as probes to search for biological macromolecules that may bind to it in the target database with known structures, and then predicting the potential targets of the drug. The convenient and fast predictive function of reverse docking provides a vital role for the discovery of drug targets, and undoubtedly, it is an indispensable tool in the process of drug research and the modernization of traditional Chinese medicine (TCM).
Compared with traditional docking methods, the reverse docking process requires more intensive calculations, for the need to process a large number of protein targets. And, a large number of docking calculation has higher requirements on the scoring function. Optimizing the energy threshold and using different scoring functions for comprehensive evaluation will be more suitable for reverse docking.\textsuperscript{5, 6} For the characteristics of reverse docking, it is more suitable for identifying the target of a given ligand in a large number of receptors. Therefore, we can discover new targets for existing drugs and natural compounds, explain the molecular mechanism of drugs, find alternative indications for drugs, and detect adverse drug reactions and drug toxicity through reverse docking.

It is known that TCM plays an important role in the long history of China, Korea, Japan, etc. And its pharmacological effects and clinical effects have been verified in practice. But the traditional pharmacological research methods can’t explain the mechanism of TCM for its complex components and elusive dose-response pattern. With the assistance of bioinformatics technology, the pharmacology of TCM has been analyzed utilizing reverse docking to deduce the molecular mechanism. Also, the analysis in terms of network pharmacology suits the study of TCM because of the characteristics that it works as multi-components on multi-targets, unlike contemporary western medicine.\textsuperscript{7} Such as matching the genic and phenotypic information related to Liuwei Dihuang, a traditional prescription for the treatment of asthenia of renal yin in China clinically, into a network to explore the mechanism of Liuwei Dihuang.\textsuperscript{8}
Herein, we show the reverse docking can not only reveal the potential new indications and toxicity of each small molecular component, but it can also accurately reveal the pharmacological action and mechanism of TCM.

1. Reverse docking

It is well known that Donepezil used for mild Alzheimer’s disease was successfully studied with quantitative structure-activity relationships. The protease inhibitor Crixivan was successfully developed through molecular simulation and chemical modification. Besides, the development of the antihypertensive drug Captopril and the anti-epidemic virus drug Zanamivir also used structure-based drug design. Presently, structure-based drug design has been widely used, and coupled with the maturity of computer data mining technology, the use of molecular docking can more accurately research the interaction between drug molecules and target proteins, and predict their binding mode and affinity. Reverse docking is based on molecular docking technology. For a given small molecule compound (natural product, lead compound, and chemical compound), reverse docking uses the molecular docking program to dock the small molecules with targets in the target database of known structure one by one and scores the stability of the binding complex. Selecting well-bound biological macromolecules as potential targets of the small molecule drugs. The work procedures of exploring the target of Betaine in the treatment of diabetes by reverse docking are shown in Fig. 1.
The basis of Reverse docking is the protein database and molecular docking program. The protein database collects information on the structure and active sites of thousands of biological macromolecules. The Protein Data Bank (PDB) is a database that contains the most protein structures and is constantly being supplemented. There are 181,969 protein structures, of which 54,060 are human protein structures up to 9 November 2021. Moreover, the information of high-resolution protein crystal structure collected in the PDB greatly improves the accuracy of virtual screening. In addition to PDB, the frequently used databases are: screening-PDB (sc-PDB), which collects proteins with high-resolution crystal structures in PDB, and can also obtain information about their ligand-binding pockets; Potential drug–target database (PDTD), collects more researched targets with good druggability, including protein structure and active site information; Therapeutic target database (TTD), which collects proteins from literature databases, and information on related diseases, mechanisms of action and ligands can also be obtained from the database.

The prediction of protein-ligand complexes is the key to successful molecular docking. Generally, under the premise of the principle of molecular dynamics or energy minimization, analyzing the flexibility of different molecules in the docking system. There are Flexible Ligand-Search Docking that only considers the flexibility of ligands, and Flexible Protein Docking that considers the flexibility of ligands and receptors. In addition, the scoring function is also an important part of the docking algorithm, which can distinguish the true binding
conformation, explore other alternative conformations, and distinguish between active compounds and random compounds. Usually, to ensure the success rate of docking, most docking methods select proteins with known active sites. 22, 23) Happily, more and more docking programs are currently available. The more popular ones are AutoDock, GOLD, FlexX, and so on (Table 1).

2. Application of reverse docking in drug repurposing and application of drug repurposing in COVID-19

In the application of small molecule drugs, pharmacologists have discovered that the efficacy of some drugs is not only limited to their indications but also has significant effects on other diseases. Sildenafil is well known for treating male erectile dysfunction. But it can also be used to treat pulmonary hypertension caused by pulmonary bronchial dysplasia in infants, Congenital Nephrogenic Diabetes Insipidus. 24, 25) Aspirin was used as a non-steroidal anti-inflammatory drug to relieve pain and treat inflammation and fever. Subsequently, it was found that aspirin can resist thrombosis and prevent ischemic cardiovascular disease. Recently, there have been more and more reports that the use of aspirin can reduce the risk of cancer. 26, 27) Thalidomide was originally found it had a good sedative, hypnotic and inhibitory effects on pregnancy. Afterward, it is found that Thalidomide can be used in the treatment of leprosy nodular erythema, chronic refractory pruritus, inflammatory bowel disease, multiple myeloma, metastatic colorectal cancer, and so on. 28-31)

Drug repositioning has been brought into focus by major pharmaceutical companies due to its lower R&D costs and nearly 30% success rate. 32) National
Institutes of Health (NIH, USA) has also initiated a program named ‘Discovering New Therapeutic Uses for Existing Molecules’ in 2012. Therefore, searching for targets that can bind to lead compounds or existing drugs and increasing the indications of drugs through reverse docking has become a hot method.  

Patrycja et al. used molecular docking methods in combination with specific phenotypic studies along with mechanistic studies to found Clotam, Celecoxib, Rofecoxib, Metformin, Sulindac, and other drugs are potential treatments for colon cancer.  

Bernard et al. found that Tofisopam used to treat anxiety can bind to phosphodiesterase 4 by using SELNERGY(tm) to reversely dock more than 2,000 biological targets. And they confirmed that Tofisopam has a certain effect on improving cognitive impairment. At the same time, Entacapone and Tolcapone for the treatment of Alzheimer's disease can also be directly bound to the enzyme InhA, which has the potential to treat multi-drug resistance and extensively drug-resistant of tuberculosis.

In the fight against COVID-19, the application of a series of old drugs, such as Chloroquine, Remdesivir, Favipiravir, Interferon, anti-AIDS and antibacterial drugs, played an important role in alleviating symptoms, and drug repurposing through molecular docking once again shines. Bhumi Shah et al. docked with 61 antiviral drugs that have been on the market or under clinical scrutiny and found that HIV protease inhibitors and RNA-dependent RNA polymerase inhibitors have the good binding ability with SARS-CoV-2 enzymes. In addition, protein synthesis inhibitor Methisazone, angiotensin AT2 receptor agonist CGP42112A,
and non-structural protein 3-4A inhibitor ABT450 may also become potential drugs against COVID-19. Efavirenz, a non-nucleoside reverse transcriptase inhibitor, is one of the most effective compounds proposed to treat COVID-19 infection. Jordaan M.A. et al. conducted a virtual screening of FDA-approved drugs that are partially similar to Efavirenz and found that Lovastatin and Simvastatin may be regarded as lead compounds for the further development of SARS-CoV-2 major protease inhibitors. Zhenming Jin et al. paid attention to the main protease (Mpro) which is a key enzyme of SARS-CoV-2. Through virtual docking and high-throughput screening, they discovered that Ebselen can bind to Mpro well from 10,000 approved drugs, clinical trial drugs, candidate compounds, and natural products. And Ebselen exhibits excellent antiviral effects.

The development of reverse docking in the field of drug repurposing has greatly accelerated the speed and accuracy of new drug development. Hopefully, that reverse docking will be fully explored and utilized, and better applied in clinical practice.

3. Reverse docking reveals adverse drug reactions of drugs

Small molecule drugs have a variety of pharmacological activities for multi-target characteristics, but they are also easy to off-target and cause toxic effects or side effects. However, adverse drug reaction is one of the main reasons for the failure of drug candidates in the stages of clinical trials. Furthermore, traditional methods are often difficult to determine the adverse drug reaction of type C,
which usually appears after long-term medication, the incubation period is long, no clear time relationship, and it is difficult to predict. Reverse docking can explain the adverse drug reaction of these drugs at the level of molecular through the affinity relationship between the drug and receptor as well the docking conformation and guides reducing toxic effects or side effects and enhancing targeting effects in drug design (Table 2).

Different from other aspects, the identification of adverse drug reaction related proteins (ADRRP) is the basis for reverse docking to discover potential toxic effects or side effects of drugs, such as gastric mucosal cyclo-oxygenase, phosphodiesterase, cytochrome P450, and so on. In addition to the target database established by the researcher, the most commonly used is the Database of Adverse Drug Reaction Target (DART) http://xin.cz3.nus.edu.sg/Group/dart/dart.asp. This is a publicly accessible database that contains comprehensive information about 147 known ADRRPs, as well as the physiological function of each protein, the corresponding agonist/antagonist/activator/inhibitor, the IC\textsubscript{50} value of the inhibitor, and the toxic effects or side effects of drug combination.\cite{40}

In Torcetrapib's research, Fan et al. used Cytoscape to establish a drug-gene interaction network and used DAVID and ToppFun to perform pathway annotation and enrichment analysis respectively. And then, they found that PDGFR, HGFR, IL-2 receptor, and ErbB1 tyrosine kinase may be direct off-target targets of Torcetrapib through reverse docking, and the microarray significance analysis of drug-treated adrenal cancer cells.\cite{41} To minimize the adverse drug reaction,
Jaundoo et al. used AutoDock 4.2, AutoDock Vina, and Schrödinger's Glide to reverse-dock 43 FDA-approved drugs for Gulf War Illness (GWI) to evaluate the interactions between drugs in the multi-drug combination therapy. Some of the FDA-approved drugs are predicted to bind to immune and hormone-related targets and care should be taken when using them in GWI therapy. Gefitinib, the first-line drug for non-small cell lung cancer, has certain side effects and complications. Nidhi Verma et al. determined the possible off-targets of gefitinib based on reverse docking and revealed the molecular mechanism of its side effects. In addition, the authors also found that gefitinib may have a positive effect in reducing brain and bone metastases. In a study of Aflatoxin B1, researchers employed computer-aided reverse docking analysis to identify putative targets of Aflatoxin B1 and Oltripraz by PharmMapper, ChemMapper, and Reverse 3D. The results showed that the clinically known toxic effects of Aflatoxin B1 are related to this molecule's strong binding affinity for key proteins involved in cell apoptosis, hormone metabolism, immune suppression, and digestive organ function. Kichul Park and Art E. Cho constructed a database including 1,078 proteins related to various diseases, and added a list of kinases, and found acetylcholinesterase, intestinal fatty acid-binding protein, type II and IV carbonic anhydrase valleys, and Amino acid dehydrogenase may be related to the side effects and toxicity of ginsenosides.

4. Application of reverse docking in research of TCM
TCM is widely used in China with a history of more than a thousand years, and its characteristics are stable action, few side effects, and high tolerance. However, the features of multi-targets, multi-pathways, and multi-components restrict the research on the mechanism of action and molecular targets of TCM, which also makes it difficult for many Chinese herbal compounds to be accepted by the mainstream international medical community. In most years, with the popularization of CADD in the field of drug development, the research of Chinese medicine has been given new vitality, shown in Table 3 and Fig. 2.

Some researches focus on a single active component of TCM. Niu et al. analyzed the interactions between the active anti-ischemic components of *Pterocypsela elata* and their protein targets by reverse docking based on their three-dimensional structures via the DRAR-CPI server.\(^{(46)}\) To reveal the effect of Gross saponins of *Tribulus terrestris L.* fruit (GSTTF) against ischemic stroke, Guo et al. found the active compounds of GSTTF can bind to HSD11B1 (PDB ID: 6NJ7) and AR (PDB ID: 5JJM) by molecular docking.\(^{(47)}\) Moreover, Chen et al. discovered the anti-stroke effect of benzoinum may depend on its active ingredients [(E)-3-(4-hydroxy-3-methoxyphenyl) prop-2-enyl] (E)-3-phenylprop-2-enoate, Coniferyl diangelate, and ZINC020409704 can bind well with 3 targets (PDE4D, ACE, TTR).\(^{(48)}\) And Dengqiu Xu, Jingwei Jiang et al. reversely docked catalpol with six proteins that regulated human muscle cell differentiation and fibrosis and found that catalpol has a strong binding force with TAK1. Catalpol can reduce muscle cell fibrosis by inhibiting TAK1 phosphorylation.\(^{(49)}\)
Meanwhile, there are also many studies on Chinese medicine compounds, which are based on the drug-drug similarities in structure and efficacy, and take into account the multiple interactions of target molecules and biological effect molecules in the body. The commonly used databases of Chinese herbal medicine active ingredients are shown in Table 4. Buyang Huanwu decoction (BHD) and Hua-Feng-Dan (HFD) have been used in the treatment of ischemic stroke for centuries. Qiuyan Guo et al. obtained the potential targets of 411 compositive compounds contained in BHD by the large-scale reverse docking and then built the pharmacological networks of BHD to reveal its pharmacological mechanisms. And Ping Yang et al. also clarified the active ingredients of HFD by reverse docking with the anti-stroke related targets (CASP8, CASP9, MDM2, CYCS, RELA, and CCND1). 50, 51) Likewise, Shuxuening injection (SXNI) is commonly used to treat ischemic stroke. Qian Cui et al. analyzed the binding capacity between the core compounds of SXNI and the key targets by reverse docking and constructed a Compound-Target-Pathway network of SXNI to clarify its specific molecular mechanisms. 52) Exploring the effective ingredients in TCM is a convenient and reliable way to find anti-stroke drugs. Gualou Guizhi decoction (GLGZD) is used in clinical therapy of sequela of cerebral ischemia stroke, Juan Hu et al. docked 248 small molecule compounds of GLGZD with NR2A, NR2B, FKBPI2, and Calmodulin to discover the potential inhibitors for the treatment of stroke. 53) Besides, to get candidate anti-stroke compounds from TCM, Jia-Qian
Liu et al. computationally analyzed more than 60000 compounds from the TCM database, and then docked them to the 15 known anti-stroke targets. 

During the COVID-19 epidemic, Integrated therapy of Chinese Medicine (ITCM) plays an important role in improving clinical symptoms. Quyuan Tao et al. successfully discovered baicalein and quercetin, the top two compounds of Huashi Baidu formula (HSBDF), have high affinity with Angiotensin-converting enzyme 2 (ACE2) by constructing a compound-target network to support HSBDF treat the patients with severe COVID-19 in China. Liang-Qin Gao et al. retrieved TCM monomers that act on 3C-like protease (3CLpro) and ACE2 receptors from the TCM Systems Pharmacology Database and Analysis Platform (TCMSP), and verified them by reverse docking using Autodock Vina software, and found 16 prescriptions of TCM, 5 formulas that were frequently used to anti-COVID-19 and a pair of core drugs of Forsythiae Fructus-Lonicerae Japonicae.

5. Conclusion Remark

The emergence of reverse docking technology has largely changed the mindset of new drug development, which makes the research of drug mechanisms and adverse reactions more convenient, and speeds up the process of drug marketing. However, in terms of molecular docking methods, it is impossible to strictly calculate the free energy of protein-ligand binding because the scoring function currently used is still very inaccurate. And the current molecular docking research has not considered the flexibility of the receptor protein. It is because that existing molecular docking programs still have great difficulties in dealing with
the problem of protein flexibility. These programs have to deal with the flexibility of hundreds or thousands of different proteins during the docking process, which is bound to greatly increase the amount of calculation, and the prediction results may not necessarily be improved. Therefore, the current virtual screening approach based on molecular docking is far from being used for accurate prediction. It can only narrow the possible protein targets from a large database to a smaller range and then determine it through experimental methods.

For reverse docking research, besides a large number of docking calculations, the macromolecular target database is also the most critical factor that affecting the docking results. The resolution of the protein structure affects the accuracy of the docking results. Only high-resolution protein crystal structures can be more accurately docked; Secondly, for a specific protein, multiple structures can bind multiple ligands and representative conformations with binding sites in the PDB. The choice of protein conformation is also a factor that restricts the accuracy of reverse docking. Thence, a powerful database of the target protein is an important requirement of reverse docking.

In the field of drug development, the application of reverse docking technology is undoubtedly a revolutionary breakthrough. However, only by continuously enriching the target database, improving the docking algorithm, and combining technologies such as artificial intelligence or big data, can reverse docking constantly burst into vitality and become a truly useful tool for drug discovery.
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Table 1 Molecular docking programs

| Programs  | Optimization                      | Scoring function                                                                 | URL of software acquisition                               |
|-----------|-----------------------------------|----------------------------------------------------------------------------------|------------------------------------------------------------|
| AutoDock  | Genetic algorithm                 | Semi-empirical free energy evaluation function                                  | http://vina.scripps.edu/                                   |
| Vina 59]  |                                    |                                                                                  |                                                            |
| Glide 60] | System search                     | Semi-empirical free energy evaluation function                                  | https://www.schrodinger.com/products/glide                  |
| Dock 61]  | Fragment growth                   | Molecular force field, surface-matching score, chemical environment-matching score| http://docking.org/                                        |
| Flex X 62] | Fragment growth                   | Semi-empirical free energy evaluation function                                  | https://www.biosolveit.de/SeeSAR/#FlexX                    |
| Surflex 63| Genetic algorithm                 | Molecular force field                                                            | http://www.biopharmics.com/products.html                   |
| Slide 64] | System search                     | Semi-empirical free energy evaluation function                                  | https://kuhnlab.natsci.msu.edu/software/slide/             |
| Gold 65]  | Genetic algorithm                 | Semi-empirical free energy evaluation function                                  | https://www.ccdc.cam.ac.uk/solutions/csd-discovery/Components/Gold/ |
| ICM-Dock 66] | Stochastic global optimization   | Semi-empirical free energy evaluation function                                  | http://www.molsoft.com/gui/startdock.html                  |
| MVD 67]   | The guided differential evolution algorithm (MolDock) | piecewise linear potential (PLP)                                                | http://molexus.io/molegro-virtual-docker/                 |
| Fred 68]  | System search                     | Geometric matching score, semi-empirical free energy evaluation function         | http://www.eyesopen.com/                                  |
| Drug            | Target                                                                 | Adverse drug reaction                                           | Docking program          |
|-----------------|------------------------------------------------------------------------|-----------------------------------------------------------------|--------------------------|
| Torcetrapib 41) | Platelet-derived growth factor receptor, hepatocyte growth factor receptor, Interleukin-2 receptor and ErbB1 tyrosine kinase | Activated aldosterone system and induced hypertension            | CDOCKER                  |
| Gefitinib 43)   | Mitogen-activated protein kinase 10, Serine/threonine-protein kinase pim-1, Dihydrorotate dehydrogenase, Receptor tyrosine-protein kinase erbB-4 and Serine/threonine-protein kinase CHK1/2 | Nausea, vomiting, diarrhea and interstitial lung disease         | Glide 6.9                |
| Aflatoxin B1 44) | Cyclin-dependent kinase 1/2, androgen receptor, estrogen receptor, sex hormone-binding globulin, glucokinase and glycogen synthase kinase-3 β | Hepatotoxicity, affects the hematologic, immune, reproductive, and digestive systems | PharmMapper, ChemMapper and ReverseScreen3D |
| Melamine 69)    | Glutathione peroxidase 1, Beta-hexosaminidase subunit beta, l-lactate dehydrogenase A chain and Lysozyme C | Nephrotoxicity and lung toxicity                                  | INVDOCK                  |
| Ibuprofen 70)   | Catechol O-methyltransferase, adipocyte lipid-binding protein, estrogen sulfotransferase, Extracellular regulated kinase 2 and arginase | Hypertension, Altered lipid distribution, sexual dysfunction, Enhanced mitogenic effect and Hyperammonemia | INVDOCK                  |
| Clozapine 71)   | Ribosylhydronicotinamide dehydrogenase, myeloperoxidase, alpha-tocopherol transfer protein and hsp70 | Agranulocytosis                                                   | DOCK                     |
Table 3 Application of reverse docking in TCM

| Drug                                      | Active components                                                                 | Target                                                                                                           | Indications                      | Docking program        |
|-------------------------------------------|------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|----------------------------------|------------------------|
| *Pterocypsela elata* 46)                  | Lactuside B, 11β, 13-dihydrolactucin acetate, and 11β, 13-dihydrolactucin         | Glucocorticoid receptor, Carbonic anhydrase 1, Plasminogen, Angiotensin-converting enzyme 2, Nitric oxide synthase, Afamin, Calmodulin-1, Aldo-Keto Reductase Family 1 Member C1 and NRH: quinone oxidoreductase2 | Ischemic stroke                 | DOCK                   |
| *Tribulus terrestris L. fruit* 47)        | Gross saponins                                                                     | Hydroxysteroid 11-Beta Dehydrogenase 1, Androgen receptor, Prostaglandin E synthase and Tyrosine-protein phosphatase non-receptor type 1 | Ischemic stroke                 | AutoDOCK               |
| *Benzoinum* 48)                           | [(E)-3-{4-hydroxy-3-methoxyphenyl]prop-2-enyl] (E)-3-phenylprop-2-enolate, propyl cinnamate, Coniferyl diangelate, and ZINCO2040970 | Angiotensin-converting enzyme 2, cAMP-specific 3',5'-cyclic phosphodiesterase 4D and Transthyretin          | Ischemic stroke                 | Discovery Studio and LigandFit module |
| *Hua-Feng-Dan* 50)                        | Beta-sitosterol, luteolin, baicalein, and wogonin                                  | G1/S-specific cyclin-D1, CASP8, CASP9, Transcription factor p65, E3 ubiquitin-protein ligase Mdm2 and Cytochrome c | Stroke                           | Autodock               |
| *Buyang Huanwu decoction* 51)             | Stigmasterol beta D glucoside, Medroxyprogesterone, Levistolide, galloylpaeoniflorin | Vitamin D3 receptor, Mineralocorticoid receptor, Heat shock protein HSP 90-alpha, Vitamin D3 receptor, Glucocorticoid receptor and Sodium/potassium-transporting ATPase subunit alpha-1 | Stroke                           | eHiTS docking module  |
| *Gualou Guizhi decoction* 53)             | 1N4, Trichosanthin, FK-506, Gallotannin, Glycyrrhizic acid, Gallotannin            | Glutamate receptor 2A 2B, Peptidyl-prolyl cis-trans isomerase and Calmodulin                                   | Stroke                           | eHiTS docking module  |
| Shuxuening injection | Quercetin, luteolin, kaempferol, diosmetin, catechin, chryseriol, isogoyvyrol, sesamin | Prostaglandin G/H synthase 2, CASP3 and Nitric oxide synthase 3 | AutoDOCK vina |
Table 4 Active ingredient database of TCM

| Database | Content                                                                 | Coverage                                                                 | URL                                                                 |
|----------|-------------------------------------------------------------------------|--------------------------------------------------------------------------|----------------------------------------------------------------------|
| TCMD     | Chinese medicine compound information, Chinese herbal medicine and Disease information | More than 50,000 prescriptions, more than 1,400 diseases and their medications, more than 22,000 Chinese herbal medicine, and more than 19,700 chemicals in Chinese herbal medicine | http://www.chemcpd.csdb.cn/scdb/main/tcm_introduce.asp                |
| CNPD     | Compound information, biological activity, plant source                | More than 10,000 kinds of chemical components, involving more than 4500 kinds of Chinese herbal medicine | http://pharmdata.ncmi.cn/cnpc/                                       |
| TCMSP    | Information on Chinese herbal medicine, compound information, and target information. | The 499 herbs registered in Chinese pharmacopoeia (2010), with a total of 12144 chemicals | https://tcmsp-e.com/                                                  |

TCMD: TCM Composition Database, CNPD: Chinese Natural Product Chemical Composition Database.
Fig. 1. Schematic representation of reverse docking process, an example of exploring the target of Betaine in the treatment of diabetes.
(Color figure can be accessed in the online version.)
Fig. 2. Schematic diagram of using reverse docking to analyze Chinese medicine compound.
(Color figure can be accessed in the online version.)