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Exploring the Multi-level Interaction Mechanism Between Drugs and Targets Based on Artificial Intelligence

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ABSTRACT

With the improvement of people's living standards and the increasing emphasis on health, new and higher demands are also placed on the medical industry. The diagnosis and treatment methods combining artificial intelligence and medicine are bound to receive more and more attention and promotion. At present, drug design is stepping into the era of artificial intelligence, and academia and industry are actively applying artificial intelligence technology to all aspects of drug research and development, including drug screening, molecular characterization, drug activity and druggability optimization, chemical reaction design, etc. Relying on the big data information of millions of patients, the artificial intelligence system can quickly and accurately mine and screen out suitable drugs. Through computer simulations, artificial intelligence can make predictions about drug activity, safety, and side effects, and find the best drug that matches the disease. This technology will shorten the drug development cycle, reduce the cost of new drugs and improve the success rate of new drug development.

As a researcher, I am responsible for the research on the "intersection of artificial intelligence and medicine". During my tenure, artificial intelligence is used for drug discovery and drug design. Systematic research on the interaction mechanism between drugs and targets, drugs and diseases, and drugs and pathways has been carried out from different levels of single molecule-single target, single molecule-multi-target, and multi-molecule and multi-target.

KEYWORDS: Artificial intelligence; Drug design; Single molecule; Single target; Multi-molecule; Multi-target

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Single Molecule-Single Target Drug Action Mechanism

Single-molecule drugs refer to small molecule compounds that are artificially synthesized and highly selective to targets, which are usually called targeted drugs. The study of the interaction mechanism between single molecule and single target is the most important and difficult step in drug research, which has positive significance for drug design research. However, compared with the time-consuming and expensive experimental approach to reveal the interaction mechanism between molecules and targets, computational simulation is a more convenient and efficient way. Molecular simulation technology plays an increasingly important role in the development of new drugs. In our project, we explored the interaction mechanism between single molecule and single target by combining multiple molecular simulations [1]. The model constructed in our study can not only predict the biological activity value of drugs quickly and accurately, but also help researchers to better understand the binding mode of drugs and targets to design drugs with higher activity and fewer side effects [1].

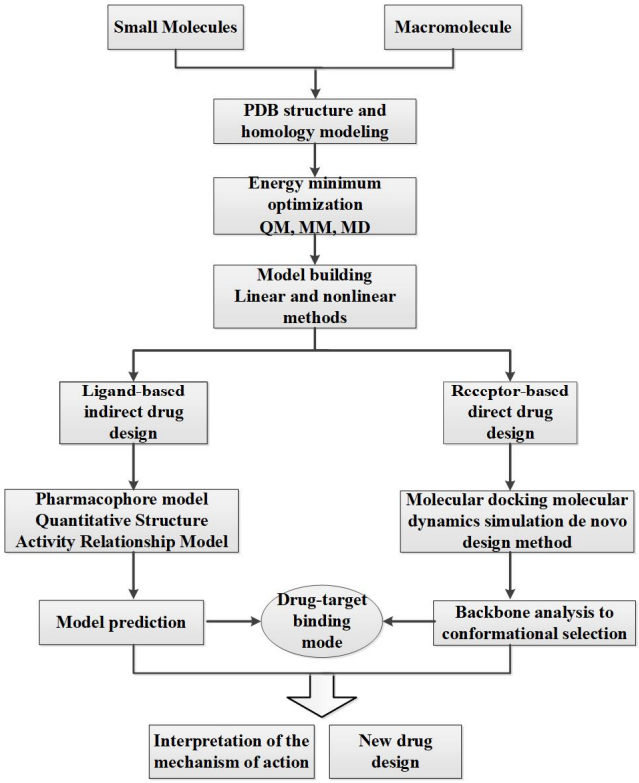

Figure 1. Schematic diagram of the single molecular and single target action mechanism

In addition, we also apply genetic algorithm to the establishment of 3D-QAR model, and prove the rationality and feasibility of GA method [2]. The GA method realizes the segmentation of the entire data set into a training set and a validation set using an algorithm program. The established model has good stability and robustness and can accurately predict the activity of drug molecules, which improves the efficiency of constructing the model. GA improves the modeling method of three-dimensional quantitative structure-activity relationship from single molecule and single target level, and can design new and highly active drug molecules more quickly and efficiently in drug design.

Finally, in my current study, I used machine learning and deep learning algorithms in artificial intelligence to conduct in-depth research on 33 human cancer types in the TCGA database and big data on the pathological and molecular characteristics of 17,000 malignant tumor samples and corresponding normal tissues from more than 10,000 patients, and used a variety of algorithms, including independently trained artificial

intelligence models, to filter, normalize, and classify biological sequences in these samples. Then, machine learning models were trained with these data to distinguish different cancer types, different stages of the same cancer type, and to distinguish between tumors and normal tissues. It is expected to find new therapeutic targets from key factors such as tumor microenvironment, autophagy, methylation, pyroptosis, immune checkpoint, ferroptosis and copper death, so as to provide a basis for in-depth study of tumor development mechanism, diagnostic markers, therapeutic targets and new drug design.

We used AIDD, CADD, molecular simulation, computational chemistry and chemical informatics to systematically study the interaction mechanism between drug molecules and targets from the perspective of single molecule-single target, which has important reference value for redesigning new lead compounds based on structure, so as to achieve rapid lead design and development.

Single Molecule-Multi Target Drug Action Mechanism

Monomeric drugs have a variety of medicinal properties, such as anti-oxidation, anti-cancer, antibacterial and other effects, which are an important source of new drug development. Nearly 200 kinds of modern drugs are directly or indirectly derived from natural plants, including flavonoids, polyphenols, alkaloids, terpenoids and other structural types. They have high medicinal value and are useful tools for screening drugs from traditional Chinese medicine. More than 50 % of currently available drugs are derived directly or indirectly from natural products. Therefore, the discovery of new compounds in herbal medicines will help to develop new therapeutic drugs for western medicine.

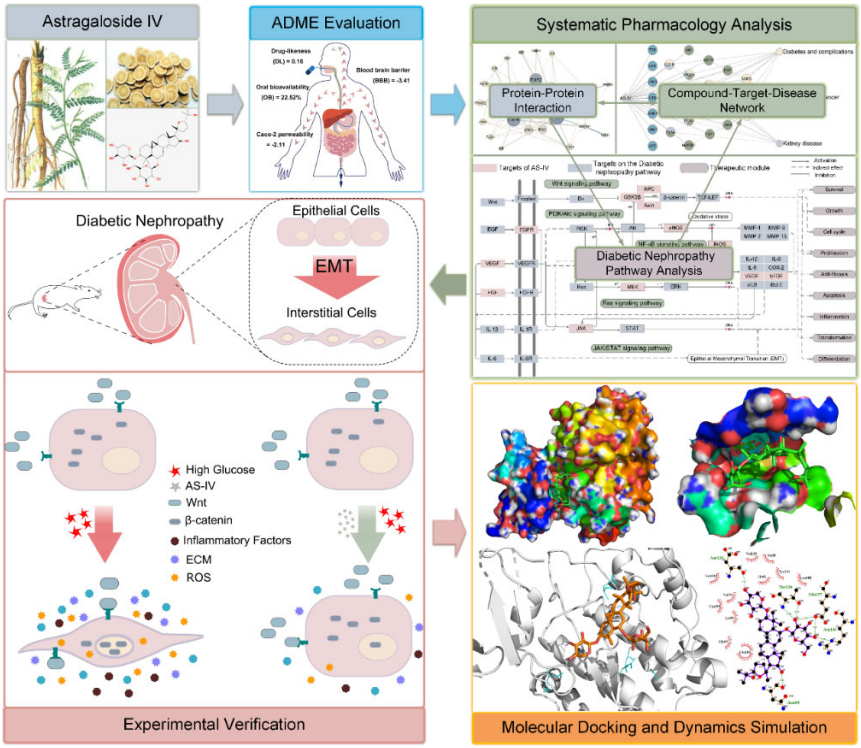

Figure 2. Multi-scale analysis of the mechanism of AS-IV in the treatment of DN [3]

In this project, we demonstrated that herbal monomer Astragaloside IV can inhibit neuroinflammation in the brain by acting on multiple targets and repair synaptic plasticity to improve memory impairment in mice. At the same time, we also confirmed that Astragaloside IV has anti-oxidative stress, anti-inflammatory, anti-epithelial-mesenchymal transition, and can ultimately improve the high glucose-induced kidney damage. Therefore, we systematically elucidate the multi-target mechanism of Astragaloside IV. Overall, for the first

time, we systematically analyzed the mechanism of action of AS-IV by using systematic analysis methods, providing new theories and methods for studying monomer.

We systematically analyzed the mechanism of action of Astragaloside IV by using systematic analysis methods, providing new theories and methods for studying monomers of botanicals, and potentially indicate a new therapeutic approach.

Multi Molecule-Multi Drug Action Mechanism

Multimolecular drugs refer to botanical drugs that contain multiple monomeric compounds. Natural botanical medicine is a complex chemical composition system, its material basis is composed of a variety of components, and these components are not simply stacked, they have a certain composition and quantity ratio within and between components. These components produce synergistic effects through multi-target, multi-pathway and multi-level integrated regulation. However, the components of botanical drugs are complex. Each botanical drug may contain multiple components, and each active component may act on multiple targets. This feature makes it extremely difficult to study the mechanism of plant drugs.

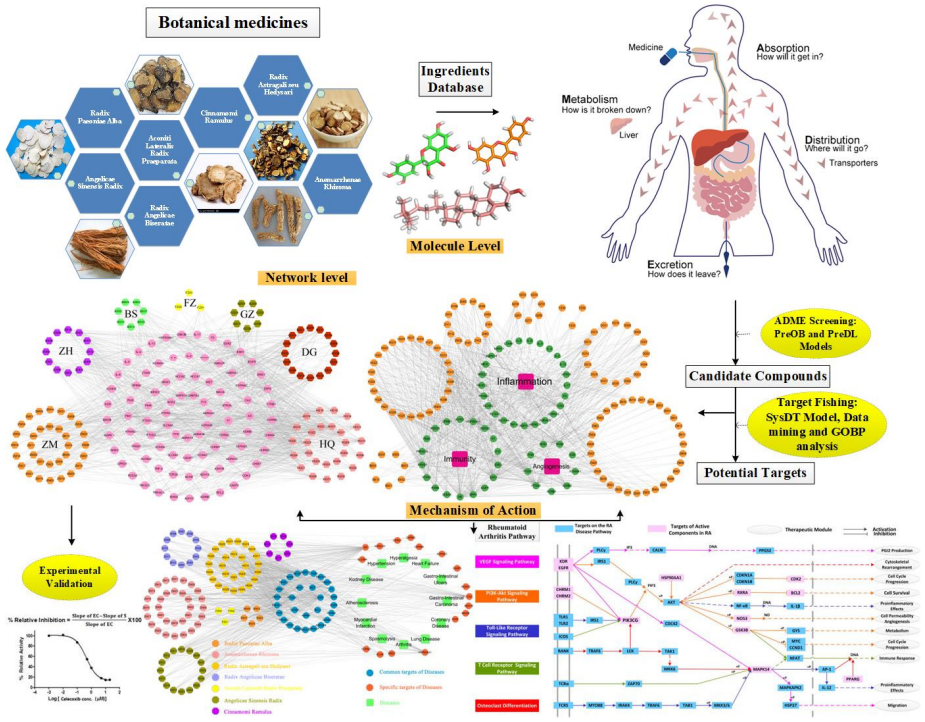

Figure 3. Work scheme of systems pharmacology approach [4]

In order to solve this problem, in this project we constructed a plant medicine research system and framework. We constructed a pharmacokinetic screening model based on the AI algorithm, and then constructed a database of plant drug targets based on the screening results. Based on the deep learning algorithm, we constructed the drug-drug interaction relationship between the active components of plant drugs. Finally, we verified the relationship between drugs and targets based on dry and wet experiments at the molecular level. At the same time, we also studied the auxiliary efficacy and mechanism of action of classical botanical drugs in tumors. Obtaining chemical components of botanical drugs through big data search and mining. Then the active components and targets were obtained by machine learning method, and the targets were verified and screened by molecular docking and binding free energy analysis, so as to obtain the targets of botanical drug pairs in the treatment of tumors. Further analysis of the target corresponding to the biological function, disease and related signaling pathways, and then explain the multi-component, multi-

target, multi-pathway mechanism of botanical drugs in the treatment of cancer.

We also tried to use statistical methods to construct a new multiple botanical drug compound and explain its mechanism of action. Comprehensive data mining of the database was carried out by artificial intelligence algorithm, and diseases and botanical drugs were used as search terms to screen botanical drugs significantly related to diseases. Because different drugs are studied to different degrees, a statistical index defined by the P-value-supergeometric cumulative probability distribution is used here to assess whether there is a statistically significant correlation between drugs and disease. When $P \leq 0.01$, it is considered that the botanical drug has a significant correlation with the disease. In addition, based on some clinical medication experience, a botanical drug compound significantly related to the disease was finally obtained. Finally, the applicant also used system pharmacology, bioinformatics, computational chemistry and experimental verification to explain the mechanism of action of new botanical drugs. Through multi-level analysis and experimental verification of drugs, targets, pathways and diseases, the synergistic mechanism of botanical drug compound and the biological basis of the disease were expounded [4].

We developed a systematic research framework technology that integrates drug ADME screening, target recognition, network construction, pathway enrichment, and drug-disease association analysis. The framework integrates biological network modules, artificial intelligence, machine learning, computational chemistry, molecular dynamics, molecular thermodynamics, and combines chemical genomics, reverse molecular docking, and data mining interactive supplements to obtain targets and combine ' dry and wet ' experimental verification to ensure the accuracy and reliability of the method for obtaining targets of botanical drugs active ingredients. At the same time, based on the drug-target network and animal models, using a variety of molecular biology methods, through theoretical speculation and experimental verification, the molecular mechanism of multi-component and multi-target of botanical drug compound was revealed from the whole animal, tissue organ and molecular protein level. It provides an exemplary research method for the study of the mechanism of action of botanical drugs and the development of new drugs.

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