Concept Design of Computer-Aided Study on Traditional Chinese Drugs

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Traditional Chinese drugs (TCDs) have played a key role for Chinese people in the treatment of diseases since ancient times. The use of TCDs has generated a great amount of information in the past thousand years about the relationship between natural products and the human body. However, up to now, our understanding on the mode of action of the TCD is still limited. Considering that the basic mechanism of all drug function involves the interaction between the drug and biological receptors at the molecular level, we propose to connect TCDs with modern medicine theory through molecular structures. We propose to explain functions of TCDs by using the knowledge developed in modern molecular biology, pharmacology, computer chemistry, and biochemistry. We are working on a computer-aided Chinese drug study that is discussed in this paper. A short introduction on the progress of our research is also given.

1. INTRODUCTION

Traditional Chinese drugs (TCDs) have many advantages, such as apparent efficacy in the treatment of many diseases and cheap production and use. For these reasons, TCDs are widely used today, occupying around 45% of the market in China. At present, 12 694 species of natural products are used as drugs in China.[1] Among them, there are 11 020 medicinal plants, 1590 medicinal animals, and 84 medicinal ores.

It is apparent that to treat diseases, the ancient people tried many different natural products, such as herbs, animals, and ores, as medicines, because there were no other effective options. To their surprise, and also that of many of us, the natural products worked well enough in the treatment of diseases. Even though we do not have a good understanding about how the traditional medicines work, an essential point is that the basic principle of the actions of TCDs and Western drugs (WDs) are the same, that is, the interactions between the medicinally active molecules of TCDs or WDs and their biological receptors at the molecular level provide therapeutic functions on diseases. Many effective components of TCDs have been isolated from plants, and their biological activities in vivo and in vitro have been examined.[2−7] For example, the medicinal plant *Lonicera japonica Thunb*. has been widely used in TCDs as an antipyretic for the treatment of fever, carbuncles, inflammation, etc., and contains the effective component chlorogenic acid. Modern pharmaceutical studies show that chlorogenic acid has many functions; it is an antioxidant and a chemopreventive agent for large bowel carcinogenesis; it inhibits hepatic glucose 6-phosphatase, the nitration of tyrosine, epidermal lipoxygenase, and tongue carcinogenesis induced by 4-NQO; it has inhibitory effects on gastric ulcers and mutagenicity of Trp-P-1 and Glu-P-2, and a blocking effect on *N*-nitrosomorpholine formation in vitro; and it may be effective not only in protecting against oxidative damage but also in inhibiting potentially mutagenic and carcinogenic reactions in vivo. *Angelica sinensis (Oliv.) Diels*, one of the most widely used TCDs, is used as a tonic medicine for the treatment of anemia, asthenia, and the deterioration of the functions of organs. One effective component of *Angelica sinensis (Oliv.) Diels* is ferulic acid. Biological assays indicate that ferulic acid is an antioxidant and chemoattractant; it inhibits carcinogenesis and murine interleukin-8; it has antimicrobial, antibacterial, antifungal, antimutagenic, and anti-HIV activities; and it has positive effects on fertile and asthenozoospermic infertile human sperm, etc.

Conventionally, in treating a disease, Western medical researchers tend to find a single drug (a pure chemical) for one biological target. For some cases, the method works well, but for others it does not. Modern medicinal studies reveal that a disease may relate to many different kinds of biological receptors. In the field of cancer study, Barinaga[8] stated that "The research efforts of the last 20 years have laid out a host of targets for these new drugs, such as, tyrosine kinase inhibitors for receptors of platelet-derived growth factor (PDGF) and epidermal growth factor (EGF), farnesyl transferase inhibitors for preventing ras activity, cyclin-dependent kinase (CDK) inhibitors for blocking cell cycle, etc." Therefore, if we have different drugs that can attack all or most targets related to a disease, the possibility of achieving success in curing the disease should be much higher than if only one target is attacked. A striking point is that a dose of a TCD may be able to attack many different targets simultaneously, while it also contains components that can reduce the toxicity of the drug. A basic idea of TCDs is the compatible application of drugs; that is, the use of several different natural products in one dose of TCD, with each of them playing some different function. For example, in recent years, a dose of an anticancer drug may contain up to 20 different natural products to obtain the best therapeutic effect.[9] The main objective of traditional Chinese medicine (TCM) doctors for each patient is to find a set of natural products that works best when the products are used together.

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Many trials may be needed in searching for the best combination of natural products. The types and quantities of natural products may be changed considerably based on the situation of each patient and the progress of his disease.

It should be noted that a great diversity of chemicals exists in natural products. For example, the database NAPRALERT File,[10] developed by College of Pharmacy, University of Illinois at Chicago, contains more than 110 000 chemicals derived from natural products. The diversity of natural products provides the possibility that TCDs or other traditional drugs may contain sufficient types of molecules to treat different diseases effectively.

On the other hand, TCDs are still in the developing process, and our understanding of them is still very limited. The authenticity of TCDs is not fully supported by modern medicine theories. In particular, the mode of action of TCDs is not clearly elucidated at the molecular level. Therefore, the value and functions of TCDs are not widely realized and accepted, as yet. To improve the understanding of TCDs from the stage of philosophy and experience to the level of modern medicine should be extremely valuable, not only for the use of TCDs, but also for the development of modern medicine theories. Considering the vast accumulation of knowledge in the fields of biology, pharmacology, computer chemistry, biochemistry, etc., we propose to use computer chemistry as a bridge to link TCDs with modern medicinal theory and knowledge. In this paper, we mainly discuss the concept design of the computer-aided study of TCDs.

2. FOUNDATIONS OF COMPUTER-AIDED STUDY OF TCDS

In modern drug research, computers have assumed very important roles in the study of molecular structures and activities; for examples, in storing, retrieving, and displaying molecules, and in calculating interaction energies between drugs and their bioreceptors.[11−13] Many databases and modeling programs have contributed to the foundation of computer-aided drug design. For example, the Brookhaven Protein Data Bank (PDB) contains 7157 biopolymer crystal structure data,[14] and has the key information for understanding protein, DNA, and RNA structures and their interactions with small molecules. The Cambridge Structural Database (CSD) contains 181 037 crystal structures of organic or organometallic compounds,[15] and is an important tool for studying the structures of small molecules. The NCI database (National Cancer Institute, National Institutes of Health, USA) contains >400 000 three-dimensional (3D) molecular structures,[16] and has been widely used in searches for lead compounds in computer-aided drug design. Databases with a great number of protein and nucleic acid sequences and other information have been developed, and some of them can be retrieved through the Internet.[17,18] Molecular mechanics and quantum mechanics (including semiempirical quantum mechanics) methods can provide very helpful information on molecular structures and interaction energies.[12,19] In short, a great amount of medicinal information has been obtained through long-term research on biological systems and drugs at the molecular level. Nowadays, the computer is one of the necessary tools in many aspects of modern medicinal studies, but applications of computers in the mechanistic study of TCD is almost absent. Therefore, it would be very helpful in improving our understanding of TCDs if we could connect the wealth of modern medicinal information and the study of TCDs through use of computers (Figure 1).

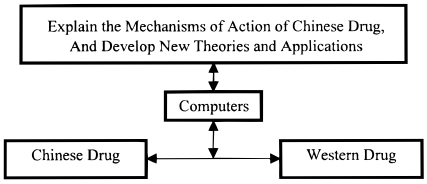

Figure 1. Connection of Chinese drugs and Western drugs and explanation of the mechanisms of action of Chinese drug with computers.

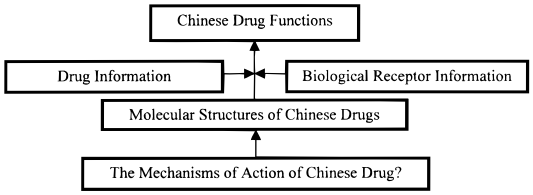

Figure 2. Study of the mechanisms of action of Chinese drugs with molecular structures isolated from TCD and modern medicinal information.

The theoretical basis for building the relationship between TCDs and modern medicine is the basic principle that all drug actions are due to the interactions between drugs and their biological receptors. Hence, it should be possible to deduce the functions of TCDs if there is enough information on TCD that can be linked to modern medicine (Figure 2).

There are many questions that should be clarified to understand Chinese drugs. We think that two questions are key and they could be answered to some extent based on the knowledge of TCDs, modern medicine, and computer technology. The two questions are:

1. What are the biological functions of each chemical component existing in a TCD? For every molecule in a TCD, no matter whether it is effective, its biological functions should be known for a full understanding of the effects of a dose of a TCD. The knowledge of the chemical components of TCDs has been greatly improved because of the intensive research work performed worldwide. We estimate that around 10 000 compounds existing in TCDs have been identified and reported. Among these, >1000 active components of TCDs have been carefully studied. However, for most among the 10 000 compounds there is almost no information on their biological activities. A method that can be used to obtain helpful information for these components depends on the analysis of structural similarity with the molecules whose biological activities are known.

2. How do the many different molecules in a dose of Chinese medicine interact with the multiple receptors in the human body and how do they achieve their integrated effect? This question concerns the mechanisms of interaction between many kinds of molecules and many kinds of biological receptors. To answer this question, a knowledge of drug interactions is essential. Up to now, there have been numerous reports concerning the drug interactions of pairs of molecules. This question could be answered to some extent if systematic analytical work can be performed based on the known clinical information of TCDs and drug interactions.

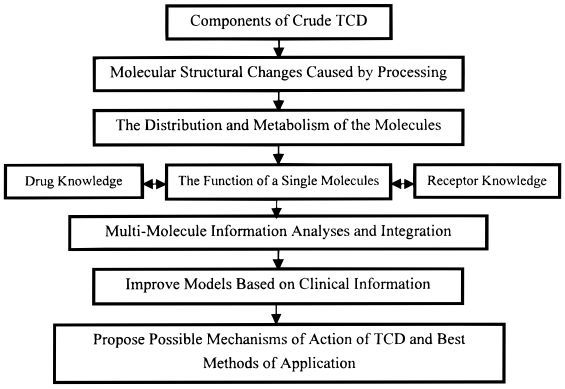

Figure 3. The basic scheme of computer-aided study of TCDs.

3. THE BASIC SCHEME OF COMPUTER-AIDED STUDY OF TCDS

Computer-aided TCD study is a new field, and extensive investigation is needed to have a deep understanding of this field. From our analysis, the basic scheme for computer-aided TCD study is described in Figure 3.

Computer-aided study of TCDs relates a great amount of research work and knowledge; information, databases and research should be collected, built and performed:

A. Molecular Information System of TCDs and Modern Drugs.

- Knowledge base of medicinal effects of each molecule
- Two-dimensional (2D) and 3D structural information database
- Biological receptor knowledge base (including enzymes, DNA, RNA, etc.)
- Knowledge based on transferring, distribution, and metabolism of TCD molecules
- Knowledge base of TCD molecular toxins
- Physical and chemical properties

B. Systematic Analyses of Molecules Isolated from TCD.

- If there is no biological information on the molecules isolated from a TCD, perform molecular structure similarity analyses by comparing with the molecular structures whose pharmaceutical functions have been studied. In this way, the possible functions of some molecules of the TCD may be deduced.
- If the molecules of TCD are similar to the known drug structures or to key substructures of the drugs and there are crystal structures of the drugs complexed with their biological receptors, further studies on the binding abilities and interaction energies between the molecules of a TCD and the receptors can be conducted.

C. TCD Information System.

- Therapy information on TCD
- Toxicity information on TCD
- Other information, such as collection locations, processing methods, etc.
- Assess the biological functions in the human body of each molecule in a dose of the TCD.

D. Systematic Analysis of a Dose of TCD.

- Based on the information just presented, a study of the interactions between the many different components in a dose of a TCD and biological receptors in the human body; and a summary the mechanisms of action of the TCD.

4. CURRENT PROGRESS AND CONCLUDING REMARKS

We are working on the molecular information system of TCDs, which includes the main information needed for TCD mechanistic studies (e.g., physical and chemical properties, molecular structures, pharmacology, clinical application data, etc.). We have finished the definition of the information system of the network version and the programming of the system's prototype with functions for displaying structures and pharmaceutical data, etc., developed statistical programs, artificial neural networks and genetic algorithms, and a 3D structure searching program. At present, our Molecular Structure Database of TCD (MSDT) contains >4000 molecular structures of compounds isolated from plants, herbs, animals, fungi, etc. The molecular structure database is managed by the software ISIS/BASE.[20]

As a test, the MSDT is being used in a study of the antihypertensive (AHT) functions of 116 most widely used Chinese drugs (plants, herbs, animals, fungus, etc.). Some 108 possible pharmacophores, extracted from 11 classes of AHT drugs that have been used clinically or studied by modern medicinal methods, and five possible pharmacophores from Chinese AHT drugs are used as query structures for a 2D search of MSDT. This search was made to determine which of these Chinese drugs contain AHT molecules and what kinds of functions they may have. The results show that flavone compounds may be the main AHT molecules in TCDs. The second main AHT compounds in the TCDs may be those that modulate the storage and release of nerve transmitter substances. These TCD molecules, identified by the MSDT search, do not definitively possess AHT functions, but it is worth paying attention to them when the TCDs are used in treating diseases. Furthermore, the information from the search can be used as a valuable reference in understanding the functions of the Chinese drugs. An interesting point according to the literature is that some Chinese drugs are associated with AHT functions, yet we did not find that they contain substructures similar to known AHT drugs studied in this work. This result means that the TCDs we studied may contain new AHT lead compounds. One in depth and broader research, needed for a better understanding of these TCDs, will be reported in another paper.

The study of TCDs is in a new developmental stage in which intensive studies of TCD mechanisms are being performed while incorporating the knowledge of modern medicine. In this process, the interactions between the multiple molecules of TCDs and the multiple receptors of biological systems will gradually be clarified, the mechanisms of TCDs will be elucidated, and the applications of TCDs will be improved and extended. The computer-aided study of TCDs will be helpful in speeding up the process and finding new lead compounds. We feel that a completely new kind of Chinese drug, a modern Chinese drug (MCD), may evolve based on the integration of the immense medicinal knowledge of TCDs, WMs, and modern studying methods (Figure 4).

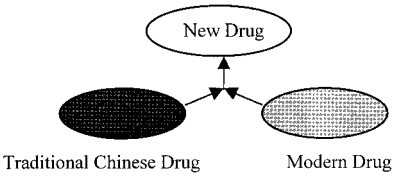

Figure 4. Development of new drugs based on the integration of the knowledge of TCDs and modern drugs.

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