Natural Small Molecule Drugs from Plants

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Preface

Natural medicines refer to substances that exist in nature and are used as drugs for the prevention and treatment of diseases, including minerals, plants, microorganisms, and animals. Natural medicines are the earliest drugs used for the treatment of human diseases and play an important role in the development of human being. Natural medicines have become important materials used to protect the health of humans after long-term accumulation of application. The formation and development of medicine science is also grounded in natural medicine. Chinese traditional medicine was originated from long-term accumulating experiences of using natural medicine by Chinese people. Up to now, a large number of chemical drugs used in clinic are still from natural products. These small-molecule compounds derived from natural substances are also called natural medicine.

In the long history of natural medicine, it was greatly promoted in different drug applications and need for clinical drugs. To obtain ideal drugs and new natural medicines and to achieve better therapeutic effects, medical scientists had done a lot of researches and modified them, which promoted the development of medicine science. Drug tablets, medicine, and modern formulations in Chinese traditional drugs reflected the development of pharmaceutical science.

The modern pharmaceutical sciences have led to the understanding of composition and mechanisms of natural medicines. With the progress of modern medicinal chemistry, a large number of natural medicines with defined molecular structure were used as clinical drugs. It is common characteristic of drugs to elucidate its compositions and mechanisms at the molecular level. Therefore, natural medicine moves to a new stage. It is the basic requirement of modern drug research to obtain valuable compounds from natural products.

The progress of medical science, the development of life sciences and the breakthrough of biology provide new theories and techniques for drug research. People who understand the role of drugs at the molecular level explore and discover many new drugs. Especially, various types of compounds from natural products including biological macromolecules enriched the resources of drug research and development and provided more new drugs for the treatment of diseases in clinic, which bring a positive effect and good results. Therefore, modern natural medicine mainly

refers to drugs derived from natural substances, such as minerals from inorganic compounds and trace elements, antibiotics from microbial microorganisms, biological macromolecules from microorganisms and animals, and small-molecule compounds from plants.

Small-molecule compounds which were derived and isolated from plants are presented in the book. The development history and characteristics of these drugs are reviewed as well. The mechanisms of these small-molecule drugs from natural products are elucidated, which provide support for clinical drugs and provide guidance for the study and development of natural medicine by summing up experiences of research.

Natural Medicines Are a Kind of Important Substances for Prevention and Treatment of Human Diseases

Modern natural drugs are named synthetic chemicals. Natural medicines are drugs which exist in nature. These drugs can be obtained by artificial methods, but since these compounds exist in the natural product, we still call them natural medicine. According to research, modern drugs are divided into macromolecule and small-molecule drugs according to their structure, which showed their basic characteristics and provided guidance for research and development. Therefore, there are also small-molecule and macromolecule drugs in natural medicine, such as hormones (small-molecule drugs) extracted from animals and proteins including insulin (macromolecule drug) obtained from animals.

Structures of macromolecules are complex. They are mostly derived from natural products, such as plants, animals, and microbes. In recent years, a large number of macromolecules were obtained by application and integration of many techniques, especially manual design and biosynthesis, such as antibody drugs, protein drugs, peptide drugs, polysaccharide drugs, DNA and RNA, etc. These drugs brought good results in clinic. With the rapid development of life sciences and biological technology, biological macromolecule drugs will become the most rapid field in research and development of modern drug.

At present, most of chemical drugs used in clinic are small-molecule drugs, which have been studied for more than 100 years. There are detailed mechanisms and a lot of experiences about these drugs, which provided strong support for these drugs in treating diseases.

Up to now, small-molecule drugs used in clinical were divided into three categories according to their sources: (1) those natural small-molecule drugs which were directly separated and purified from natural products, (2) those which were obtained by modifying structure of natural small-molecule drugs that accounted for a large proportion in clinical drugs, and (3) those that are obtained through chemical synthesis. It is obvious that natural products can not only be used as drugs but also provide important structural information in drug research and development.

Therefore, in drug discovery, it is very important to study history of natural small-molecule drugs.

The development and progress of chemical technology provide a strong support for the research of natural products. Scientists can obtain more and more natural compounds with new structure, good activity, and good prospects from natural products. More important drugs would be discovered for diseases by studying these compounds.

Natural Medicine Is the Foundation of Modern Pharmacy

Natural medicines refer to substances which exist in nature. The major sources of natural medicines are minerals, plants, microorganisms, animals, and so on. Obtaining natural medicines from these natural resources is critical for drug development. Currently, natural chemical drugs used in clinic are also derived from many sources, such as minerals, plants, microorganisms, animals, and so on.

Natural Small-Molecule Drugs Derived from Minerals

Major drugs that are used in treating diseases caused by micronutrient deficiencies originate from minerals such as inorganic compounds and some specific elements. Some active minerals in human body are also used as important drugs to treat diseases, such as arsenic trioxide used to treat leukemia, calcium carbonate used to supplement calcium, and iron compounds used to treat iron deficiency anemia. In addition, a large number of chemical elements including zinc, copper, selenium, mercury, manganese, etc., are also used in clinic.

In traditional Chinese medicine, many minerals which play important roles in the development of traditional medicine and in clinic are recorded. Forty-six kinds of mineral drugs, such as realgar, arsenic, gypsum, and so on, are recorded in *Shennong's Classic of Materia Medica* which is a classical book about pharmacy in China. Most of those traditional drugs are still used for treating diseases today.

Natural Small-Molecule Drugs Derived from Microorganisms

In the history of modern chemical drugs, drugs derived from microorganisms play important roles in treating diseases. These drugs which reflected great progress in fighting human diseases occupy a large proportion of natural medicine in type and quantity. In particular, the discovery of antibiotics opened up new areas of developing drugs from microbes. A large number of antibiotics not only are widely used in the treatment of diseases infected by bacteria but also function as antiviral,

anti-pathogenic microorganism, and antitumor agents. In addition to a lot of antibiotics, a number of new drugs with extensive roles are also obtained from microorganisms, such as antibiotics treating cancer and some drugs which were developed from fungi including *Ganoderma lucidum*, *Cordyceps*, *Poria*, and ergot and used to regulate physiological functions. These drugs have played very important roles in improving human health.

Microbes have been used as drugs for long time by human being, such as some fungi, bacteria, and even pathogens. Particularly, the research and development of antibiotic drugs was greatly promoted by the discovery of penicillin and its successful application in treating infectious diseases. The discovery of antibiotic prevented death of humans caused by infectious diseases, which is a great progress of medicine. Small-molecule drugs derived from microorganisms, which are one of the important sources of many drugs, not only have diverse chemical structures but also physiological and pharmacological activities.

Natural Small-Molecule Drugs Derived from Animals

Thousands of years ago, humans realized that some substances obtained from animals could be used to treat diseases. These small-molecule drugs, such as adrenaline, glucocorticoid, pituitrin, and dopamine, play important and even indispensable roles in the treatment of serious diseases. In addition, macromolecules in animal body, such as insulin, also play important roles in treating diseases. Using modern molecular and biological techniques, people have developed a large number of artificially manufactured "natural substances," such as proteins, peptides, polysaccharides, nucleotides, antibodies, and so on. These biological drugs have become an important part of modern drug research.

Animals are also one of important drug sources. Sixty-seven drugs derived from animals were recorded in *Shennong's Classic of Materia Medica*. Most of drugs derived from animals are obtained through extraction and preparation, including a substantial portion of macromolecule drugs which are important contents in modern biotechnology drug research. Small-molecule drugs derived from animals are also of important value, especially the discovery of hormonal drugs and neurotransmitter drugs, which not only provides new type of drugs for clinic but also promotes the progress of pharmaceutical theory. The discovery and application of glucocorticoid not only save many lives of patients with serious diseases but also contribute to knowledge of process in hormone regulating organism. Small-molecule drugs derived from animals, represented by epinephrine and acetylcholine, open up a novel field of life science research and improve the effectiveness of many serious diseases, such as hypertension, diabetes, and so on.

Natural Small-Molecule Drugs Derived from Plants

Small-molecule compounds from plants have the characteristics of various types, diversity structures, many activities, and stable resources. Those with strong pharmacological effects and clinical efficacy have been widely used to treat human diseases in clinical. They have attracted great attention of drug researchers, which are the major content described in the book.

Natural small-molecule drugs derived from plants are a large class of drugs. Small-molecule drugs are very abundant for there are numerous species of plants. Therefore, plants are major sources of natural medicine. The book is focused on small-molecule drugs from plants.

The 2015 Nobel Prize of Physiology or Medicine was awarded to the Chinese scientist Prof. Yoyo Tu for her outstanding contributions in the discovery of artemisinin. This award has also attracted attention to the development of small-molecule drugs from plants, which has become an important research field of pharmaceutical science.

Up to now, natural small-molecule drugs that are used in clinic have underwent long processes of research and development, such as artemisinin. Every drug was successfully obtained by continuous research and development, which reflected the development and progress of pharmaceutical science. Therefore, it is important to sum up the mechanisms and research processes of natural small-molecule drugs from plants, which provide experiences for the research and development of new drugs and guidance for the comprehensive evaluation of the characteristics and application prospect of natural medicine.

The Research and Development of Natural Small-Molecule Drugs Embraces the Wisdom of Humans

During the history of natural small-molecule drugs, the experience and wisdom of fighting diseases was recorded by humans. The discovery of every drug underwent a hard process of exploration and even a long process of development. These processes not only provided important references in technology for research of new drug but also had important significance in knowledge and theory of drugs.

The success of natural small-molecule drugs from traditional drugs represented by artemisinin, etc., showed great achievements in the development of traditional Chinese medicine and proved the effectiveness of traditional drugs and the controllability of material basis, which meets the requirement of modern drug. Especially, the research and development process of artemisinin gave us more inspiration. The research and development processes of drugs are hard, and the need for drugs to

treat human diseases is eternal. Therefore, exploring and finding new drugs will never end. Previous success and failures are very useful for research and development of new drugs.

Technological progress is an important guarantee for the success of drug development. There are many difficulties in the early research of natural small-molecule drugs, such as its separation and extraction, analysis, identification, and activity evaluation. All these need the support of corresponding technology. Currently, chemical nature and structures of many natural small-molecule drugs used in clinic, such as metformin, paclitaxel, vinblastine, and so on, were elucidated after 10 years or even decades of efforts. Up to now, techniques for modern separation, purification, and analytical technology were greatly improved. It isn't difficult to obtain natural small-molecule drugs any more. However, how to find better drugs is still a big scientific question that we need to consider.

Scientific methods and correct thinking are important conditions for the success of research. Historical experience is of great value to understand and develop natural medicine. For example, the discovery of vitamin C went through a long process of research and development. First of all, it was realized that humans will suffer from scurvy due to lack of ascorbic acid intake by analyzing a large number of seafarers' death. Furthermore, people found that intake of fruits and vegetables could improve symptoms of the disease. In spite of this, people still couldn't avoid forming the wrong guiding ideology in preventing and treating the disease. People even attributed the cause of scurvy to lack of "acid" in the body. Based on this ideology, absurd treatment including taking diluted sulfuric acid or acetic acid to prevent scurvy among seafarers were emerged, which not only caused more death from this disease but also delayed the discovery of ascorbic acid for hundreds of years. Therefore, correct thinking and guidance are vital in the discovery and development of new drugs.

The history of natural small-molecule drug research embraced the wisdom, knowledge, experience, technology, and spirit of medicine science exploration, which is an important reference and significant guide for drug research.

Small-Molecule Drugs Derived from Plants Are the Representatives of Natural Medicines

Plants have been used as drugs by humans to prevent and treat diseases for a long time. Humans had a lot of experiences in using plants to treat diseases before the ancient civilizations, which were recorded in literatures of ancient civilizations in the world. This is mainly due to the fact that plants are much easier to be obtained than other substances and that varieties of plants can have many different activities and become an important source of obtaining drugs.

Small-molecule compounds are secondary metabolites derived from plants. Their production and metabolism reflect the vital processes of life science and have

some biological functions, which are reflected by some ways in human body. Some small molecules have an important function in plants and important pharmacological effects in the treatment of diseases.

Small-molecule compounds derived from plants are the foundation of drug development. Small molecules have properties of rich and reliable sources. Both natural collection and planting can be easily achieved. The study of small-molecule drugs derived from plants needs complex techniques, methods, and scientific theories in many disciplines and fields, such as botany, chemistry, biology, life science, etc., which reflected progress of science and technology. Research and development of small-molecule compounds derived from plants can promote the overall scientific and technological level of drug research.

Features and Instructions of the Book

1. Drugs with the following characteristics are presented in the book: ① earliest drugs which were collected in the national pharmacopoeia or national standard and drugs which were used in clinical before and replaced by new alternative medicines now, ② small-molecule drugs directly derived from plants without structural modification or modified drugs without change of major properties, ③ drugs consisting of a variety of small molecules derived from plants, and ④ compounds collected as standard by pharmacopoeia and never directly used as a drug in the form of a monomeric compound.

   This book illustrates that the development of modern pharmacy was promoted by small-molecule drugs derived from plants. The book provides an overview of natural small-molecule drugs derived from plants for researchers in pharmaceutical field.
2. One hundred twenty kinds of drugs are discussed in the book. There are seven chapters that discuss about drugs and their clinical use, such as drugs for cardiovascular diseases, drugs for diseases of metabolism, drugs for neurological and psychiatric system, drugs for immune inflammatory diseases, antitumor drugs, and drugs for parasites and bacterial infection. Vitamins were described in the sixth chapter and the seventh chapter mainly mentions drugs collected only as reference compounds in the pharmacopoeia. The classification is made only for convenient reading. In fact, some drugs have various pharmacological effects, so the classification may not be completely reasonable. However, these drugs are described in detail according to their characteristics. The chapter about vitamins only limits its discussion on those vitamins derived from plants, which does not reflect the whole topic about vitamins. The same class of drugs is sorted according to the first word of their Chinese names. Multiple drugs from the same plant are introduced together to facilitate readers' understanding of the whole situation.

   In addition, for small-molecule drugs, the plant which was firstly found and used as a major source of drugs is introduced.

3. The book introduces every drug from many aspects, such as name, alias, Chinese and English chemical name and structure, physicochemical properties, formulations and indications, source records, development history, pharmacological effects, clinical application, comprehensive content evaluation, references, and so on. Every drug is collected in the pharmacopoeia and its physicochemical properties are briefly described in the book. The development of research and pharmacological activity of every drug are described to help readers' comprehension. The introduction of each drug had no more than ten references, including the earliest and latest published articles, which are most important in the research of drug to help readers understand the whole process.

The book is written by persons who are first-line researchers, teachers, and clinical doctors working in the field of pharmacy and pharmacology. Every drug is described by about 3000 easy-to-understand words, which are accurate in expression of pharmacy knowledge. The book provides guidance and reference for researchers, teachers, and clinical doctors.

The drugs discussed in the book are only small-molecule drugs from plants without natural medicines from other sources. Due to the limited knowledge of authors, there are a lot of omissions and errors in the book. Please don't hesitate to point them out if you find any.

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