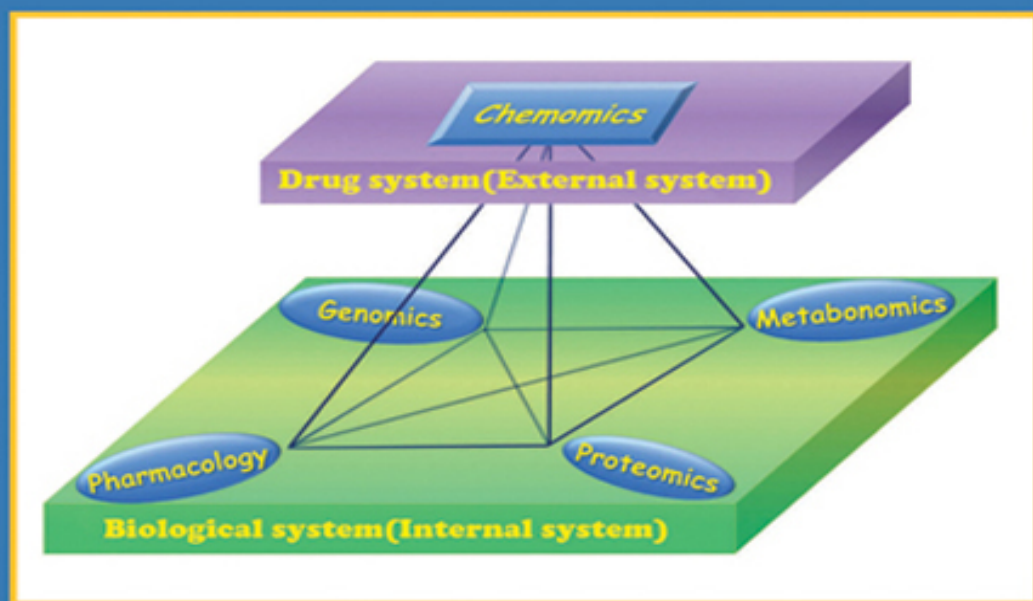


SYSTEMS BIOLOGY FOR TRADITIONAL CHINESE MEDICINE



GUOAN LUO
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Table of Contents

[Cover](#)

[Title page](#)

[Copyright page](#)

[FOREWORD](#)

[PREFACE](#)

[ABBREVIATIONS](#)

[CHAPTER 1 INTRODUCTION OF SYSTEMS
BIOLOGY IN TRADITIONAL CHINESE
MEDICINE \(TCM\)](#)

[1.1 CHARACTERISTICS AND COMPATIBILITY
PRINCIPLES OF TRADITIONAL CHINESE MEDICINE
\(TCM\)](#)

[1.2 KEY SCIENTIFIC ISSUES IN TCM
MODERNIZATION](#)

[1.3 DEVELOPMENT OF SYSTEMS BIOLOGY](#)

[1.4 CHEMOMICS INTEGRATED SYSTEMS BIOLOGY](#)

[1.5 RESEARCH STRATEGY AND PROSPECTIVE OF
SYSTEMS BIOLOGY IN TCM](#)

[CHAPTER 2 CHEMOMICS OF TRADITIONAL
CHINESE MEDICINE](#)

2.1 CHARACTERISTICS AND RESEARCH
DIFFICULTIES IN TCM

2.2 BACKGROUND OF TCM CHEMOMICS'
PROPOSAL AND DEVELOPMENT

2.3 CHEMOMICS

2.4 CHEMOMICS AND THE RESEARCH OF
FORMULAS

CHAPTER 3 TECHNOLOGICAL PLATFORM OF TCM CHEMOMICS

3.1 ACQUISITION METHODS AND TECHNIQUES
FOR TCM CHEMOMICS

3.2 CHARACTERIZATION TECHNIQUES OF
CHEMOME-TCM FINGERPRINTING

3.3 INFORMATION PROCESSING FOR THE STUDY
OF TCM CHEMOMICS

3.4 DEVELOPMENT OF AN INTELLIGENT QUALITY
CONTROL SYSTEM IN THE PROCESS OF CHINESE
MEDICINE PRODUCTION

CHAPTER 4 PHARMACOKINETIC INVESTIGATION ON TCM FORMULAS BASED ON GLOBAL SYSTEMS BIOLOGY

4.1 PHARMACOKINETIC CHARACTERISTICS OF
TCM FORMULAS

4.2 METHODOLOGY OF PHARMACOKINETICS OF
TCM FORMULAS

4.3 APPLICATION OF PK-PD MODEL IN THE
TOXICOLOGICAL RESEARCH OF *LIUSHEN* PILLS
(LSP).

4.4 PROSPECT

CHAPTER 5 APPLICATION OF GENOMICS IN THE RESEARCH OF TCM

5.1 GENOMICS AND TCM SYSTEM RESEARCH

5.2 PROSPECT OF GENOMICS IN TCM RESEARCH

5.3 CASES OF THE APPLICATION OF GENOMICS IN TCM RESEARCH

CHAPTER 6 PROTEOMICS STUDY OF TCM

6.1 PROTEOMICS IN TCM RESEARCH

6.2 A CASE STUDY OF PROTEOMICS IN TCM

6.3 THE APPLICATION OF HIGH CONTENT SCREENING IN TCM RESEARCH

6.4 LIMITATIONS AND PROSPECT OF TCM PROTEOMICS

CHAPTER 7 APPLICATION OF METABONOMICS IN RESEARCH ON TCM

7.1 CURRENT RESEARCH SITUATION OF METABONOMICS

7.2 INTEGRATION OF QUANTITATIVE METABONOMICS PLATFORM TECHNOLOGY (QMPT)

7.3 APPLICATION OF METABONOMICS IN THE FIELD OF MEDICINE

7.4 EXAMPLES OF METABONOMIC RESEARCH ON TCM

CHAPTER 8 APPLICATION OF CHEMOMETRICS AND BIOINFORMATICS IN TCM RESEARCH

8.1 INTRODUCTION OF CHEMOMETRICS

8.2 CHEMOMETRIC TECHNIQUES AND THEIR
APPLICATIONS IN TCM RESEARCH

8.3 INTRODUCTION OF BIOINFORMATICS

8.4 BIOINFORMATICS TECHNIQUES AND THEIR
APPLICATIONS IN THE RESEARCH OF TCM

8.5 CONCLUSIONS

CHAPTER 9 STUDY OF INTEGRATED BIOMARKER SYSTEM OF DIABETIC NEPHROPATHY

9.1 INTRODUCTION OF DIABETIC NEPHROPATHY

9.2 MOGENSEN STAGING AND TCM TYPING OF DN

9.3 THE METABONOMICS STUDY OF DN

9.4 CONDITION OF METABOLISM AFTER
TREATMENT WITH *TANGSHEN* FORMULA (TSF)

9.5 GENOMICS STUDY OF DIABETIC NEUROPATHY

9.6 THE INTEGRATED BIOMARKER SYSTEM OF DN

9.7 CONCLUSIONS

CHAPTER 10 CHEMOMICS RESEARCH ON THE TCM FORMULA OF THE *QINGKAILING* INJECTION

10.1 CHEMOMICS RESEARCH OF *QINGKAILING*
INJECTION

10.2 PHARMACODYNAMIC EVALUATION OF
QINGKAILING INJECTION

10.3 RESEARCH ON THE *QINGKAILING* DERIVED
FORMULA

10.4 CONCLUSIONS

CHAPTER 11 INTEGRATED GLOBAL SYSTEMS BIOLOGY FOR THE RESEARCH AND DEVELOPMENT OF CHINESE MEDICINE *SHUANGLONG* FORMULA

11.1 BRIEF INTRODUCTION TO THE *SHUANGLONG*
FORMULA

11.2 CHEMOMICS STUDY OF THE *SHUANGLONG*
FORMULA

11.3 PHARMACODYNAMIC EVALUATION OF SLF
EFFECTIVE INGREDIENTS

11.4 SYSTEMS BIOLOGY STUDY OF THE
MECHANISM OF DIRECTED DIFFERENTIATION OF
STEM CELLS INDUCED BY NSLF6

11.5 ANTI-MYOCARDIAL INFARCTION EFFECT OF
NSLF6

11.6 CONCLUSIONS

CHAPTER 12 DEMONSTRATIVE RESEARCH ON THE SAFETY EVALUATION OF *LIUSHEN* PILLS

12.1 INTRODUCTION

12.2 TOXICITY STUDY OF *CHANSU*

12.3 CHEMOMICS STUDY OF LSP

12.4 ASSESSMENT OF EFFECTIVENESS AND
SAFETY OF LSP

12.5 IN VIVO DISTRIBUTION AND METABONOMICS
OF LSP AND *XIONGHUANG*

12.6 METABONOMIC RESEARCH OF LSP

12.7 CONCLUSIONS

Index

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Published by John Wiley & Sons, Inc., Hoboken, New Jersey

Published simultaneously in Canada

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Library of Congress Cataloging-in-Publication Data:

Luo, Guoan, 1946-

Systems biology for traditional Chinese medicine / Guoan
Luo . . . [et al.].

p. ; cm.

Includes bibliographical references and index.

ISBN 978-0-470-63797-5 (cloth)

I. Title.

[DNLM: 1. Medicine, Chinese Traditional. 2. Systems
Biology. WB 55.C4]

610-dc23

2011052327

FOREWORD

Professor Guoan Luo and I got to know each other in late 1990s because of the implementation of the Fundamental Research of Key Scientific Issues in Traditional Chinese Medicine Formula project in the National Basic Research Program of China, and we have been working together in a multidisciplinary team ever since then. During more than 10 years of collaboration, I was quite impressed by his sagaciousness, enthusiasm, and modesty. He has proposed a series of new approaches and methodologies for Traditional Chinese Medicine (TCM) formula research and explained these profound theories in a simple and understandable way in this treatise. Additionally, as the backbone of our team, he encourages innovation in research and has set himself as an excellent example to his followers, which truly fulfilled the connotation of “learn to be an excellent teacher and act as an exemplary person.” As stated in his own preface, Prof. Luo is convinced that through the test of time and practice, TCM will be an advanced science, and the theories of TCM always have been, are, and always will be a guidance for its clinical practice, and vice versa. As a TCM scholar myself, not only will his remarkable contributions in theory, technology, and implements for TCM command my gratitude and admiration, but also his deep understanding and prospective assessment of TCM theories and practices as a medicinal chemist will help to promote its academic development.

Biomedical research development should be innovative as well as adaptive considering the dramatic changes in the scientific environment and the needs of public health in this new era. Therefore, medical scientists have integrated translational medicine, digital medicine, and regenerative

medicine. Translational medicine requires establishment of a “basic research-clinical practice-industry-talent” system from laboratory to clinic, from hospital to community village, and from result to benefit in order to benefit the people, which is a major livelihood project. Translational medicine also includes integrative medicine and pharmacy, so-called 3P medicine—including predictive, preventive, and personalized medicine, as well as participative medicine. According to the theory of combining natural sciences with humanities in translational medicine, some original theories and practical experiences in TCM, including the concept of holism, imagery thinking, and treatments based on syndrome differentiation, inseparability of the body and spirit, and prevention of disease, are interpreted with modern concept and then applied to research and practice so as to establish the leadership of TCM in the medical field. With the purpose of keeping the innovativeness and adaptability of TCM research on the basis of modern science, we first need the guidance of correct cosmology, for example, the “harmony between body and nature” theory that was originated from hieroglyphics and long-term agricultural civilization, and the “harmony but different” theory, which integrates macro and micro perspectives, synthesis and analysis methods, entity and relationship ontologies.

The essential processes to understand these theories and incorporate them with the Western theories include regression analysis based on systems biology, stratification research based on systematic method, and drawing of a preliminary conclusion. Second, we need to conduct interdisciplinary research. Since the era of Sir Newton and Madame Curie long ago, scientific study today requires the integration of all natural science fields, although the innovative studies following one’s own interests are still respectable. For instance, biologists or chemists can be the

leaders to manage research work. So besides personal skills, all-around consciousness, empathic ability, and humanistic literacy are more important at present. Third, we need to establish innovative teams and cultivate positive team spirit. Specifically, we call for good study and working styles, tolerance of failed attempts, and overcoming fickleness and eagerness for instant success and quick profits.

Nowadays, many intellectuals in the scientific and technological fields approve the scientific aspect of TCM; the public looks forward to its dedication to public health; and government actively supports the development of the TCM industry, so this is a perfect time for the modernization of TCM. However, there are still some problems and barriers. As a result, we should unite experts and scholars and learn as much from them as possible in all fields. For clinical medical research, the concepts and methods of scientific evidence-based medicine should be introduced to get high quality, high level, and consistent evidence in TCM and Western medicine to reflect the vitality of TCM. For basic medical research and industrial development, innovation of methodology should be treated as the first priority, and scientific hermeneutics that integrates understanding, interpretation, and application should be used to interpret the unique advantages of original theories in TCM to enrich modern medical science. Additionally, the method system should be updated by using advanced instruments and new techniques to promote the research and development of innovative TCM in order to provide services for clinical medicine and bring benefits to society.

This book is a summary of years of research by Professor Luo's expert group. Prof. Luo elaborates on the formation, evolution, and research content of systems biology for TCM, as well as insightfully analyzing the methodology system based on holism and systematology of TCM. After reading

this treatise, I noted with pleasure that there was guidance for both modern concepts and operable technical routes. This treatise is not only based on the TCM theory of prescription such as “seven conditions in making up prescription,” “*Jun, Chen, Zuo, and Shi*,” and intensive study of component compatibility and molecular biology, but also contains original thoughts on basic theories, information about product research and transformation, and updates on major prescriptions. Moreover, this treatise contains active explorations about the introduced complex intervention in refractoriness diseases, which can guide the transition from “Western learning spreading to the East” to the coexistence of both “Western learning spreading to the East” and “Eastern learning spreading to the West.” As we remember, Prof. Mi Wu and Prof. Yinke Chen from the Chinese Culture College in Tsinghua University always called for independent spirit and free thought, arguing for respecting the Chinese cultural heritage and thinking back to the old virtuous people before seeking the development of Chinese culture. Furthermore, when it comes to education, Han Yu’s “knowledge teaching, method introducing and problem solving” have been taken as the model, but only by breaking through the conservatism and advocating originality and research can academic advancements be improved.

Although Prof. Luo suggests some shortcomings about this book, his truth-seeking and difference-seeking spirit is very encouraging. In light of our profound friendship after many years of cooperation, it certainly is an honor to write this Foreword. I want to share these words with Professor Luo’s group and hope they are encouraged by them. And last, I would like to express my gratitude and congratulations to Prof. Luo for this splendid treatise.

Prof. YONGYAN WANG
Academician of Chinese Academy of Engineering
Former President of China Academy of Chinese Medical
Sciences

PREFACE

Why did we write this book about systems biology for traditional Chinese medicine (TCM)? Because we have found that systems biology is one of the best tools among modern science and technologies to embody the essence of holism and systematology-based TCM (Eastern medicine) and to modernize TCM. At the same time, the philosophy and methodology of TCM theory can also benefit and promote the development of systems biology. In this book we applied systems biology to investigate TCM and attempted to combine the essential merits of Eastern and Western medicine. We believe that the research and development of TCM should be different from the “point to point” (P2P) methodology of Western medicine (which represents a single small molecule acting on a single target), and we propose a “system to system” (S2S) methodology (which represents a drug system interacting with the human body system) in order to develop modernized composite medicine and realize the modernization of TCM.

There are similarities as well as differences between TCM-based systems biology and systems biology in general that have been defined by Professor Lee Hood, Jeremy K. Nicholson, and others. The similarities lie not only in their philosophy, where holism and systematology both describe the study of a drug's action with a body system, but also in the platform, such as genomics, proteomics, metabonomics, and bioinformatics. Systems biology was defined to be the study of how a biological system responds to a given disturbance or stimulant of the environment. When considering Western medicine, the disturbance is usually just a single compound representing the action of a point to a biological system (P2S). On the other hand, the study of

systems biology in TCM shows the interaction of a drug system to a biological system (S2S), since the formula-based medication commonly used in TCM constitutes a drug system including a mixture of numerous compounds. Biological systems including the human body could be addressed by the network of genes, proteins, or metabolites. Additionally, the therapeutics of TCM is also quite different from Western medicine. Western medicine is focused on the treatment of diseases (with a specific target), while TCM is concerned with the ill body, and defines different states of the body as *Zheng* (syndrome) consisting of a set of symptoms of both pathological and physiological states. Therefore, the introduction of systems biology to the research of TCM should embody these intrinsic characteristics of TCM with a modern approach.

The discovery of Western medicine (synthetic drugs) that is based on the P2P mode has met with great success, especially for single-factor infectious diseases. However, in recent years drug research and development face serious challenges. For example, there are still no satisfying solutions for multi-factor complex chronic diseases. Furthermore, some drugs proven to be effective for a given target have been reported to have severe side-effects and are now forbidden to be marketed. Therefore, even for the study of a single-molecule drug, we should also consider its actions on the body in a systems approach (P2S mode) with the use of network pharmacology. In the Western pharmaceutical industry, some multi-component drugs have also emerged, which have been developed based on a combination of existing drugs or a combination of targets. However, the general principle and methodology for the development of multi-component drugs or composite drugs is still in demand.

TCM has a history of thousands of years. It has a systemic theory derived from long-term clinical experience, the

philosophy of holism and systematology and the theory that man is an integral part of nature (emphasizing the harmony of the body and the environment). It also emphasizes the global balance of the body other than the simple inhibitory effect on a disease target, and on individualized therapy with medication of TCM formulae. But the system of theories of TCM expressed in words is in demand of support by evidence-based study. For example, the TCM theory of “*Zang* and *Fu* organs” (including heart, liver, kidney, and lung) is somewhat different from the understanding of the organs based on modern anatomy. One of the key issues of “TCM modernization” is how to interpret the rational principles of TCM using the tools and experimental data based on modern science and technology. If we simply use the viewpoint of conventional pharmacy, we must isolate all the constituents of a given formula (tens of compounds or even more) and interpret the interactions between each constituent and each target; then we have to find out how many constituents and targets are needed to interpret such a complex interaction. In fact it may be almost an impossible mission, and such a mode (multi-point to multi-point) is inefficient to embody the characteristics of TCM of treating the body system.

In the post-genome era, systems biology was developed, which recalls the ideas of holism, systematology, and network, and provides the possibility to build a connection between Eastern and Western medicine. We are now able to investigate the interaction of a drug system (including TCM and Western medicine) and the whole body system at the level of genes, proteins, and metabolites. In order to adapt systems biology to TCM, the point-based disturbance should be developed into a drug system (composite medicine) that can be analyzed at several levels according to the constitute complexity. Based on the systems studies, the traditional formula consisting of medicinal herbs can be simplified into

a multi-component drug that may consist of isolated partials or a compatible combination of several compounds. Similarly, synthetic drugs can also be combined into a composite drug that is considered as a drug system. The composite drugs refer to treatment drugs that are composed of multiple compounds or compound groups and are developed by combining a variety of treatment principles and under the guidance of multiple action mechanisms. These drugs can achieve the holistic optimal efficacy, rather than the best effect from the single-target.

In order to develop composite drugs, we must break through the limitation of target-based discovery and consider the whole response of the body system, which may be expressed at the basic levels such as genes, proteins, and metabolites. Therefore, the studies based on genomics (Chapter 5), proteomics (Chapter 6), and metabonomics (Chapter 7) are valuable for either the body of the diseased (viewed from TCM) or diseases of the body (viewed from Western medicine). Such omics studies provide the systematic understanding of the interaction of drug system with the body system, while the isolated studies of genes, proteins, and metabolites may lead to fragmentation of information. Therefore, we conducted an integrated study of genomics and metabonomics on the cases/controls of diabetic nephropathy (DN), in order to combine the knowledge of genes and metabolites and find the disease targets, which may provide a comprehensive and systematic understanding of the complex disease by integrating the global characterization (macroscopic) of the genetic network and the metabolic network with the specific characterization (microcosmic) of given pathways and targets. Moreover, we explored the possibility of unified expression of the body of the diseased (TCM's holistic view) or diseases of the body (Western reductive view). Taking the case of DN as an example, on one hand, the expression of

Zheng was used to characterize the pathological and physiological state of the diseased body according to TCM's view; 34 symptoms of nine syndromes were scored and taken into correlative analysis with quantitative data. On the other hand, clinical biochemical and pathological indicators were combined to characterize DN according to the Western view. To connect TCM and Western medicine on the levels of genes, proteins, and metabolites, we tried to establish a comprehensive biomarker indicator system for the characterization of DN based on the platform of integrative metabonomics (Chapter 9). We reached the following conclusions: (1) The diagnostic systems of TCM and Western medicine gave consistent conclusions on most of the patients' conditions. For example, most of severe cases considered as stage V of DN were also discriminated to be the worst *Zheng* deficiency of both *Yin* and *Yang*. (2) An integrative biomarker indicator system is more suitable for new drug discovery based on the global body condition. For Western medicine, the integration of pathological and biochemical indicators with the network of genes, proteins, and metabolites provides a better characterization of a complex disease. For TCM, the integration of pathological and biochemical indicators with a network of genes, proteins, and metabolites as well as *Zheng*-based indicators helps us to understand TCM theories and facilitate the research and development of composite drugs. (3) Some of the TCM's concepts such as *qi* that are difficult to understand may have some substantial basis. For example, our study related deficiency of *qi* with some genes related to transportation, thus suggesting the essence of TCM understanding of *qi*.

In this book, a keynote topic will be focused on the development of composite drugs (including TCM and Western medicine) with the integrated consideration of both pathological and physiological impact. Many of the existing

formulae with a compatible combination of herbs are described as *Jun* (monarch), *Chen* (minister), *Zuo* (assistant), and *Shi* (guide) and were derived based on thousands of years of clinical experience. However, it is difficult to fully understand the therapeutic mechanisms of these drugs due to their complex composition. Therefore, we propose an approach of chemomics (Chapters 2 and 3) to characterize TCM and analyze TCM formula at three levels: compatibility of herbs, compatibility of fractions, and compatibility of constituents. The first two represent a drug system that should be characterized by a combination of fingerprinting (global characterization) and multi-component quantitative determination (specific characterization) different from single-compound drugs (Western medicine). The compatibility of constituents is similar to the composite drug of Western medicine. In addition, the research and development routine of composite drugs of TCM is a process during which simplification and optimization of the compatible combination is conducted step by step based on the mode of a “system to system” interaction (Chapters 10 and 11). The research and development routine of composite drugs of Western medicine is a process during which complication and optimization occur. It represents a combination of drug compounds considering the interaction of drug systems with biological systems. In addition, development of composite drugs, including TCM and synthetic drugs, was explored.

This is a research monograph with an attempt to explore a new routine, and there are likely some limitations. Here we introduce some modern studies on TCM in China, and expect to raise more interest and collaboration in the research of TCM worldwide.

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ABBREVIATIONS

5-HT	5-hydroxyl tryptamine
AA	arachidonic acids
ACE	angiotensin-converting enzyme
AGEs	advanced glycation end-products
ANN	artificial neural networks
AR	aldose reductase
ATP	adenosine triphosphate
AUROC	area under curve of a receive operating characteristic curve
BMMSCs	bone marrow mesenchymal stem cells
CE	capillary electrophoresis
CE-MS	CE coupled with mass spectrometry
CK	creatine kinases
cMHC	cardiac myosin heavy chain
CSF	cerebrospinal fluid
cTnI	cardiac troponin I
CVDs	coronary diseases
DAG	diacylglycerol
DIP	Database of Interacting Proteins
DM	diabetes mellitus
DN	diabetic nephropathy
DPN	diabetic peripheral neuropathy
EBs	embryonic bodies
DQY-PQ	deficiency of both <i>qi</i> and <i>Yin</i> , particularly <i>qi</i> deficiency
DQY-PY	deficiency of both <i>qi</i> and <i>Yin</i> , particularly <i>yin</i> deficiency
DYY	deficiency of both <i>Yin</i> and <i>Yang</i>
ECG	electrocardiogram
ECM	extracellular matrix
ET-1	endothelin
FGF	fibroblast growth factor
GC	gas chromatography
GC-FTIR	gas chromatography coupled with Fourier-transform infrared spectroscopy
GC-MS	gas chromatography coupled with mass spectrometry
Glu	glutamic acid
GO	gene oncology
HCS	high content screening
HDG	high dose group
HDL	high-density lipoprotein

HE	hemotoxylin and eosin staining
HGP	Human Genome Project
HPLC	high performance liquid chromatography
HPLC-ESI-MS/MS	HPLC-electrospray tandem mass spectrometry
HPLC-MS	HPLC coupled with mass spectrometry
IBS	Integrated Biomarker System
IDF	International Diabetes Federation
IGF-1	insulin-like growth factor-1
IGT	impaired glucose tolerance
IL-1 β	inerleukin-1 β
IMPT	integrative metabonomics platform technology
iNOS	inducible nitric oxide synthase
ISO	isoproterenol hydrochloride
KEGG	Kyoto Encyclopedia of Genes and Genomes
KNN	K-nearest neighbor algorithm
LC-NMR	liquid chromatography tandem nuclear magnetic resonance
LC-DAD	liquid chromatography tandem photodiode array detector
LC-ICP/MS	liquid chromatography tandem plasma mass spectrometry
LC-MS	liquid chromatography-mass spectrometry
LDA	linear discriminant analysis
LDG	low dose group
LDH	lactate dehydrogenase
LPC	lyso- phosphatidylcholine
LPO	lipoperoxide
LSP	<i>Liushen</i> pills
Lyso-PC	or lysophosphatidylcholines
LPC	
MCCM	multi-component Chinese medicine; multi-component drug; modernized composite medicine
MDA	malondialdehyde
MDG	medium dose group
MDLC	multi-dimensional LC
mESCs	mouse embryonic stem cells
MHC	myosin heavy chain
MI	myocardial infarction
MMDB	Molecular Modeling Database
MRM	multiple reaction monitoring
MSCs	mesenchymal stem cells
NCBI	National Center of Biotechnology Information
NEFA	nonesterified fatty acid
NIH	National Institutes of Health
NMR	nuclear magnetic resonance

NSLF6	new <i>Shuanglong</i> formula; <i>Shuanglong</i> derived formula
NTDs	neural tube defects
NTF	neurotrophic factors
OMIM	Online Mendelian Inheritance in Man
OSC	orthogonal signal correction
P2P	point to point
P2S	point to system
PC	phosphatidylcholine
PDGF	platelet derived growth factor
PE	phosphatidylethanolamine
PG	phosphatidylglycerol
PI	phosphatidylinositol
PKC	protein kinase C
PK-PD	pharmacokinetics-pharmacodynamics
PLS-DA	partial least squares discriminant analysis
PMF	peptide mass fingerprinting
PMS	premenstrual syndrome
PN	Panax Notoginseng
PNS	Panax Notoginseng saponins
PS	phosphatidylserine
QMPT	quantitative metabonomics platform technology
RT-PCR	real time quantitative polymerase chain reaction
ROS	reactive oxygen species
RPG	remainder of ginseng
RSM	remainder of <i>Danshen</i>
S2S	system to system
SAB	salvianolic acid B
SAH	S-adenosyl-L-homocysteine
SAM	S-adenosyl-L-methionine
SIMCA	soft independent modeling of class analogy
SLF	<i>Shuanglong</i> formula
SM	sphingomyelin
SNP	single nucleotide polymorphism
SOD	superoxide dismutase
SPSS	Statistical Product and Service Solutions
STITCH	search tool for interactions of chemicals
SVC	support vector clustering
SVR	support vector regression
systems	systems of absorption, distribution, metabolism, excretion and
ADME/Tox	toxicity
TBA	total serum bile acid
TCA	tricarboxylic acid
TCM	Traditional Chinese Medicine

TGF- β	transforming growth factor- β
TGS	total ginsenosides
TLC	thin layer chromatography
TNF- α	tumor necrosis factor
TSA	total salvianolic acids
TTD	Therapeutic Target Database
TV	toads venom, <i>Chanshu</i>
UPLC-Q/TOF	ultra performance liquid chromatography tandem quadrupole/time of flight MS
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VIP	variable importance
WM	Western medicine
XCMS	various forms (X) of chromatography mass spectrometry

CHAPTER 1

INTRODUCTION OF SYSTEMS BIOLOGY IN TRADITIONAL CHINESE MEDICINE (TCM)

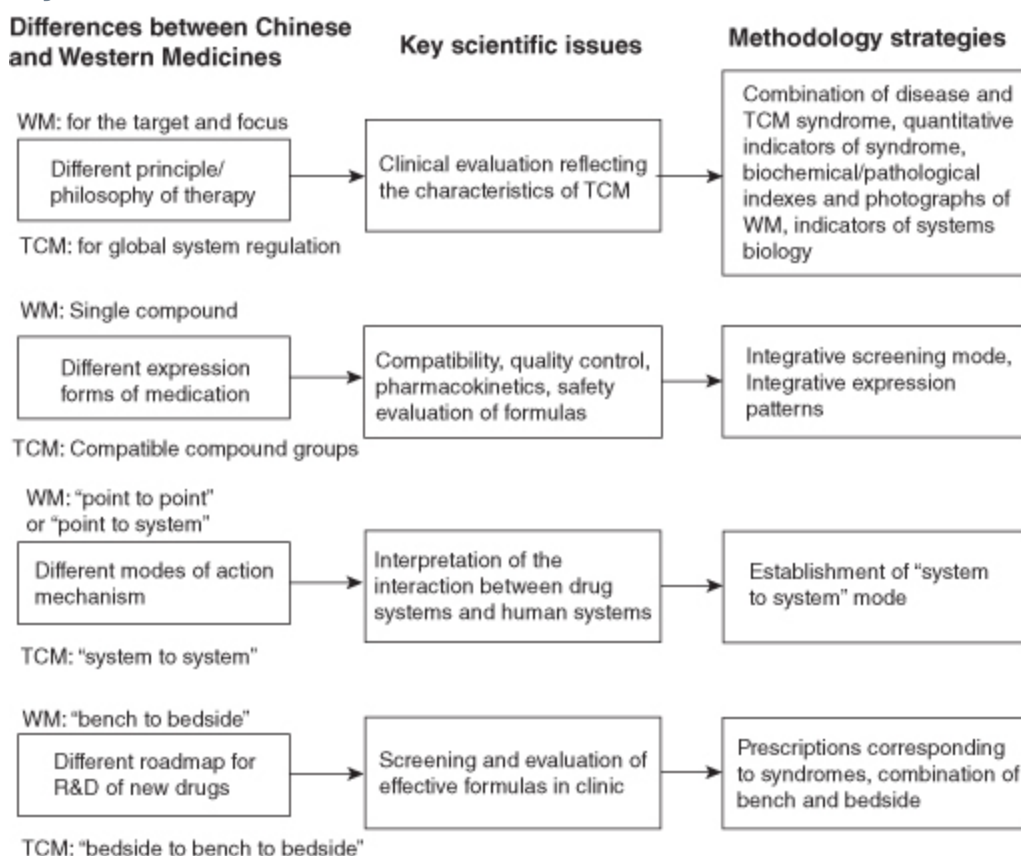
1.1 CHARACTERISTICS AND COMPATIBILITY PRINCIPLES OF TRADITIONAL CHINESE MEDICINE (TCM)

1.1.1 Special Features of Diagnosis and Treatment in TCM

Practitioners of TCM have accumulated valuable experiences in learning about life, improving health and fighting disease in its extensive history of production activities and real life practice. Chinese medicine has a unique theoretical system, rich clinical experience, and scientific ways of thinking. Based on natural sciences and the humanities and social sciences alike, it is a notable medical system in the multitudes of traditional medicines worldwide.

Eastern and Western medicines are obviously different in their treatment theories and drug forms ([Fig. 1.1](#)). These are the reflections of the differences and specialties between the East and the West. These differences cause great difficulties not only in medical communication, but also in the recognition of TCM by the Western medical system.

Fig. 1.1 Difference between TCM and Western medicine (WM) systems.



TCM has its unique treatment theory and long-term clinical experience, especially for the diagnosis and treatment of many complex chronic diseases. Meanwhile, it also faces the new challenge of inheritance and innovative development. However, the modernization and internationalization of TCM is the trend of the times. On the other hand, the Western medical system has its own problems. Therefore, practitioners of Eastern and Western medicine should learn from each other and make use of others' experiences for

reference. Through the conduction of modern research on TCM, for instance, the efficiency of TCM and its scientific value could be proved and further explained by modern scientific language through modern technology and scientific experiments, which will promote the development of TCM and modern medicine and life science as well.

1.1.1.1 Concept of Holism and System Theory

The concept of holism is the core idea of TCM theory. TCM has a unique holistic, dynamic, and dialectical theory of the complex phenomena of life and diseases. For instance, it considers the human body to be an organic integrity; the various components of body composition on body structure are indispensable, coordinating in their functions and interacting pathologically with each other. In addition, it advocates “harmony between body and nature,” and emphasizes that human activities should be adapted to geographical and seasonal changes, thus maintaining the body’s health. Meanwhile, it makes appropriate diagnoses and recommends treatments based on the overall perspective of pathogenesis, location, and potential of diseases, combined with season, geographical aspects, and diet. As a result, the holistic concept of TCM can be seen in the comprehensive and coordinative functions targeting regulation of many organs of the body. TCM formulas are based on the condition of patients; characteristics of the medication; the taste, functions, and indications of drugs; and relationships of the seven conditions of ingredients in prescription (single effect, mutual assistance, mutual reinforcement, mutual detoxication, mutual antagonism, mutual restraint, and mutual incompatibility). Prescriptions are made according to the principles of compatibility of “*Jun*, *Chen*, *Zuo*, and *Shi*” (roles of ingredients in the prescription with the functions of *Jun*, *Chen*, *Zuo*, and *Shi*, respectively).

The mutual restraint, guidance, and synergies in the process of compatibility constitute the overall effect, which is more efficient than the simple combination of each part.^[1] Professor Yongyan Wang, an expert of TCM, has stated that “TCM is not a simple allopath but an integrated regulation from the perspective of multichannels, multilinks, and multifaceted roles in the human body based on TCM formulas and the main procedure of the incidence of disease. Therefore, the human body at different levels, overall, organ, cell, subcell and molecule, can be adjusted effectively.”^[2] Moreover, the holistic concept is reflected in “the unity of medicine and treatment.” TCM formulas originate from the clinical diagnosis and are applied to the clinical diagnosis. Diagnosis, methods, prescription, and drugs are combined through the three steps of “dialectical-legislation-prescription,” and finally unified into a whole. Therefore, “systematic theory” and “holistic” ways of thinking are the essential in TCM theories, which coincide with the mainstream of modern life sciences.

The theory of “*Yin* and *Yang* balance” is the important manifestation of the concept of holism, which guides the development of TCM. In TCM, the human body is considered as a whole unit with the balance of *Yin* and *Yang* keeping a healthy condition. In TCM, we consider a disease to be caused by functional imbalance of *Yin* and *Yang*. There is a dialectical relationship between *Yin* and *Yang*. When *Yin* is too much it will lead to a deficiency of *Yang*, and vice versa (from “A Great Theory on *Yin* and *Yang* of *Su Wen*”). TCM treatment must follow the relationship between *Yin* and *Yang*, which will be regulated until the health recovers. Therefore, TCM medication is very different from the Western type. “Compatibility” is very important in TCM treatment. For example, medication should be adjusted according to the location, time, patient, and syndrome. Such a traditional theory of TCM plays an effective role in clinical