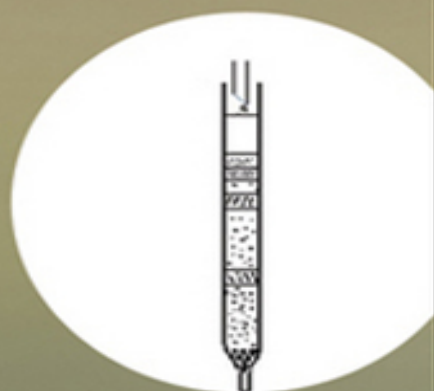
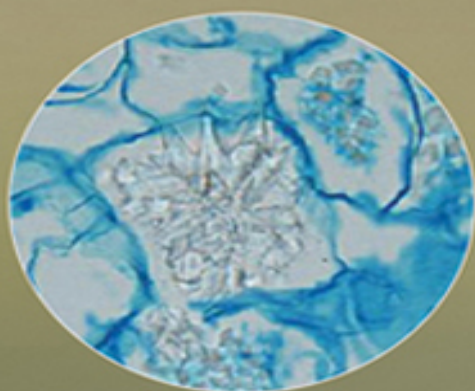
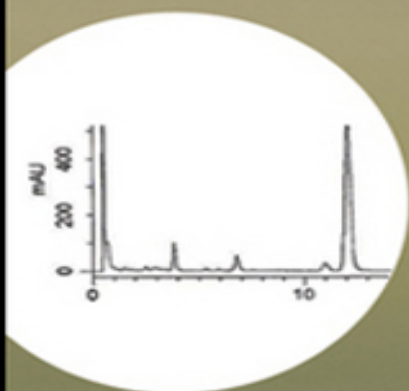


# TRADITIONAL HERBAL MEDICINE RESEARCH METHODS

*Identification, Analysis, Bioassay,  
and Pharmaceutical and Clinical Studies*



Edited by  
WILLOW J.H. LIU

 WILEY

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# **Traditional Herbal Medicine Research Methods**

## **Identification, Analysis, Bioassay, and Pharmaceutical and Clinical Studies**

Edited by

**Willow J.H. Liu**

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# ***Dedication***

*This book is dedicated to all who are interested in traditional herbal medicines and willing to make their contribution to people's health with their efforts.*

*I first want to thank all of the professors in China, Germany, and the United States who have trained me or with whom I have worked; in chronological order, they are Professor Song-Song Yang, Xin-Sheng Yao, Rudolf Bauer, Koji Nakanishi, Norman R. Farnsworth, John M. Pezzuto, Judy L. Bolton, and Gail B. Mahady. Special acknowledgment is given to all of the authors of this book for contributing their time and knowledge, as well as to Dr. Hong-Jie Zhang for introducing some of them to me. Acknowledgment is also given to all of my previous colleagues and friends who have provided me with generous academic support.*

*And most of all, I want to thank my husband, Zhuo Chen, for his understanding and all unsung support to my career, and my daughter, Emily (Chen Chen), for her time on editing this book. They have been traveling with me to different countries and cities throughout the world, accompanying me in both body and soul. This book is also a special present to my lovely little son Derek, a precious gift sent from God while I was preparing this book.*

# ***Preface***

After giving a presentation on the topic of “Modern Research on Traditional Herbal Medicine” in the American Chemical Society national meeting (September 2006, San Francisco), I received an e-mail from John Wiley & Sons asking if I would write a book with the same title.

Research on traditional herbal medicine involves botany, chemistry, biology, pharmacology, toxicology, clinical trials, and other disciplines. Chemical composition and biological or biochemical activities of many herbs have been studied by researchers in universities and pharmaceutical companies for purposes of investigation or new drug development. So far, there have been many books introducing functions or actions of herbs. Books on the chemistry of herbal medicines (often called phytochemistry), biochemistry, biology, and pharmacology of herbal medicines are also available. But there is no book giving a full description of all aspects of herbal research and development.

The purpose of research on traditional herbal medicine is not only for new drug development, but also for quality control and mechanism study of herbs. Unlike screening for new drug candidates simply using one or two bioassay tests, exploration of the mechanisms of traditional herbal medicines is much more complex. It requires close cooperation between scientists from many disciplines to unveil the secrets of the herbal kingdom. For maximal cooperation, pharmacologists, biologists, chemists, and clinical doctors need to have basic knowledge of the cooperating fields. To scientists who are very knowledgeable in modern science and have extensive research experience, their knowledge about the applications and theories of traditional medicines they are studying, for example, traditional Chinese medicine (TCM) and Ayurveda, might be limited. For this reason, their research designs for these

herbs may simply copy those for new drug development. As a consequence, the results may not be accurate due to either inappropriate design of extract methods, insufficient experiment duration in animal study, or lower concentration of samples used for bioassay tests. This is why studies using the same assay for the same herb from different labs have often reported different results.

This book introduces the methodology of collection and identification of herbal materials, extraction and isolation of compounds from herbs, *in vitro* bioassay, *in vivo* animal test, toxicology, and clinical trial for herbal research. It is not written as a literature review. Instead, it introduces the basic content and methodology of each research field and the keys for the study of herbal medicine. The purpose of this book is to help scientists who are interested in the study of traditional herbal medicine gain a broader view of herbal medicine and knowledge about its research. I hope this book can be a bridge to provide scientists in different fields with basic information and knowledge about the progress of herbal study and to help them avoid unnecessary mistakes during their studies.

As for background information on my relationship with traditional herbal medicine, I received my B.S. in Chinese Herbal Medicine, M.S. in pharmacognosy, and Ph.D. in natural product chemistry in succession from Shenyang, China. My doctoral supervisor was Xinsheng Yao of Shenyang Pharmaceutical University, a well-known phytochemist and academician in China. I left China as a professor of phytochemistry at Liaoning University of Traditional Chinese Medicine and traveled to Germany as an AvH Research fellow. There I worked in the lab of Rudolf Bauer at Duesseldorf University, a world-renowned expert in plant medicine, in particular of Echinacea, and an aficionado of Chinese herbs. I focused on bioassay screening and standardization of herbal medicines. Later I moved to New



York and worked in the lab of Koji Nakanishi at Columbia University, and then to Chicago, where I worked with Norman Farnsworth and John Pezzuto at the UIC/NIH Center for Botanical Dietary Supplement Research in Women's Health at the College of Pharmacy, University of Illinois at Chicago. The project there was the mechanism study of herbs for treating women's menopause symptoms, using *in vitro* bioassays and *in vivo* animal tests.

Unfortunately, I became afflicted with rheumatoid arthritis while I was in Chicago. My wrist gave me so much pain that I was too weak to even open a reagent bottle. Even while being treated with Western medicine, I was once paralyzed and could not get out of bed. For health reasons, I thus had to leave Chicago's harsh weather for California, and started to treat myself with Chinese herbs and acupuncture, in addition to treatment with Western medicine, while working in a research lab for pharmaceutical analysis. In my spare time, I taught Chinese herbology, TCM nutrition, as well as modern pharmacology and nutrition, at various schools of acupuncture. A few years later, I opened my own clinic of herbs and acupuncture. Since then, I have been treating patients with my combined knowledge on the functions of traditional herbs and their modern biological and pharmacological activities, meanwhile developing herbal products based on the efficacy of herbal formulas in clinical application. Research, teaching, plus clinical practice strongly consolidated my knowledge on both traditional and modern medicine, and helped me review TCM theories more deeply and from multiple perspectives.

My research on herbs in the past 25 years has told me that they work in a way that differs from modern drugs: the effect is not from one single compound in an herb, but is a synergetic result from many components working on many targets. And researchers should not be disappointed if their results show that the most bioactive compounds screened

from an herbal extract in a bioassay are popular second metabolites in plants. Examples include flavonoids, fatty acids, or amines.

The successful treatment of a variety of diseases in my clinic with Chinese herbal formulas has reminded me of what I had first learned during college: the effective treatment with Chinese herbs is mostly based on formulas composed of several or more individual herbs, rather than single ones, and the formulation of a Chinese herbal prescription is guided by theories of TCM. But most scientists conducting research on traditional herbal medicine today are either unaware of or are ignoring this.

My research in China, Germany, and the United States has extended my knowledge of phytochemistry, analytical chemistry, biochemistry, biology, and pharmacology and experience with extraction, isolation, identification, and analysis of compounds in herbs and their bioassay screening and mechanism study with *in vitro* and *in vivo* tests. This is the reason that I boldly accepted the invitation to write this book. To make each chapter in this book more authoritative, I invited several experts from different fields in China to write some chapters. In the process of editing, necessary rewriting, rearrangement, additions, and clarification of contents were made with the agreement from authors of each chapter. However, due to limited space, it is impossible to cover all aspects or give detailed information in each chapter. I hope this book will work as a guideline for new scientists working with modern technologies and help them to explore more secrets in the treasury of traditional medicines.

*Willow J.H. Liu*

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# ***Abbreviations***

*AAS*

atomic absorption spectrometry

*AEs*

adverse effects

*AFLP*

amplified fragment length polymorphism

*AFS*

atomic fluorescence spectrometry

*AIC*

Akaike Information Criterion

*ALP*

alkaline phosphatase

*AMD*

age-related macular degenerative disease

*ANOVA*

analysis of variance

*AP*

alkaline phosphatase

*APCI*

atmospheric pressure chemical ionization

*API*

atmospheric pressure ionization

*AP-PCR*

arbitrarily primed polymerase chain reaction

*APPI*

atmospheric pressure photoionization

*ASTM*

American Society for Testing and Materials



*BMD*

bone mineral density

*CAG*

coronary angiography

*CAM*

complementary and alternative medicine

*CCCD*

China Certification Committee for Drugs

*CD*

circular dichroism

*CE*

capillary electrophoresis

*CHD*

coronary heart disease

*CHL*

Chinese hamster lung cell

*CI*

chemical ionization

*CID*

collision-induced dissociation

*CIOMS*

Council for International Organizations of Medical Sciences

*CNPIC*

China National Pharmaceutical Industry Corporation Limited

*CNS*

central nervous system

*COSY*

chemical shift correlation spectroscopy

*COX*

cyclooxygenase

*CP*

cyclophosphamide

*CPC*

centrifugal partition chromatography

*CQS*

comprehensive quality systems

*DAD*

diode array detector

*DCC*

droplet countercurrent

*DEPT*

distortionless enhancement by polarization transfer

*DMEM*

Dulbecco's modified Eagle's medium

*DMSO*

dimethyl sulfoxide

*DOPAC*

3,4-dihydroxyphenylacetic acid

*DPD*

deoxy pyridinoline

*DPPH*

2,2-diphenyl-1-picrylhydrazyl

*E*

enzyme

*E<sub>2</sub>*

estradiol

*ECD*

electrochemical detector

*ECG*

electrocardiogram

*ECL*

enhanced chemiluminescence

*EFPIA*

European Federation of Pharmaceutical Industries Associations

*EI*

electron ionization

*EIA*

enzyme immunoassay

*EIS*

enzyme-inhibitor-substrate complex

*ELISA*

enzyme-linked immunosorbent assay

*ELS*

evaporative light scattering

*ELSD*

evaporative light scattering detector

*EMA*

European Medicines Agency

*ER*

estrogenic receptor

*ERB*

Ethical Review Board

*ERE*

estrogen-responsive element

*ERT*

estrogen replacement therapy

*ES*

enzyme-substrate complex

*ESI*

electrospray ionization

*EU*

European Union

*FAB*

fast atom bombardment

*FBS*

fetal bovine serum

*FC*

flash chromatography

*FCPC*

fast centrifugal partition chromatography

*FD*

field desorption

*FDA*

Food and Drug Administration

*FDCA*

Federal Food, Drug, and Cosmetic Act

*FI*

field ionization

*FLARE*

fragment length associated repair enzyme

*FOB*

functional observatory battery

*FT*

Fourier transform

*FT-ICR*

Fourier transform ion cyclotron resonance

*FTMS*

Fourier transform mass spectrometry

*GAP*

good agriculture practice

*GABA*

$\gamma$ -aminobutyric acid

*GC*

gas chromatography

*GCP*

good clinical practice

*GE*

gel electrophoresis

*GEP*

good extracting practice

*GLP*

good laboratory practice

*GMP*

good manufacturing practice

*GOT*

glutamate oxaloacetate transaminase

*GPT*

glutamate pyruvate transaminase

*GSLs*

Ginseng stem and leaf saponins

*GTP*

guanosine triphosphate

*HBV*

anti-hepatitis B virus

*HHS*

Department of Health and Human Services

*5-HIAA*

5-hydroxyindoleacetic acid

*HILIC*

hydrophilic interaction liquid chromatography

*HMBC*

heteronuclear multiple bond correlation

*HMQC*

heteronuclear multiple quantum coherence

*HPLC*

high-performance liquid chromatography

*HRT*

hormone replacement therapies

*HSCC*

high-speed countercurrent

*HSQC*

heteronuclear single quantum coherence

*HT*

serotonin

*HTS*

high-throughput screening

*HVA*

homovanillic acid

*IBS*

irritable bowel syndrome

*ICH*

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

*ICP-MS*

inductively coupled plasma mass spectroscopy

*IEC*

independent ethics committee

*IND*

investigational new drug

*IR*

infrared

*IRB*

institutional review board

*ISSR*

inter-simple sequence repeats

*ITS*

internally transcribed spacer

*JPMA*

Japan Pharmaceutical Manufacturers Association

*LC*

liquid chromatography

*LD*

lethal dose

*LDL*

low-density lipoprotein

*LH*

luteinizing hormone

*LhRh*

luteinizing hormone releasing hormone

*LIT*

linear ion trap

*LOD*

limit of detection

*LOQ*

limit of quantitation

*LPH*

lipotropic hormone

*LPLC*

low-pressure liquid chromatography

*LS*

light scattering

*LSD*

least significant difference

*MAE*

microwave-assisted extraction

*MALDI*

matrix-assisted laser desorption

*MBC*

metastatic breast cancer

*MEM*

minimum essential medium

*MHLW*

Ministry of Health, Labor, and Welfare

*MOH*

Ministry of Health

*MPLC*

medium-pressure liquid chromatography

*MRM*

multiple-reaction monitoring

*MS*

mass spectrum; mass spectrometer; mass spectrometry

*MTD*

maximum tolerated dose

*MTS*

3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium

*MTT*

3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

*MW*

molecular weight

*NAD<sup>+</sup>*

nicotinamide adenine dinucleotide

*NADH*

reduced form of nicotinamide adenine dinucleotide

*NADP<sup>+</sup>*

nicotinamide adenine dinucleotide phosphate



*NADPH*

reduced form of nicotinamide adenine dinucleotide phosphate

*NCCAM*

National Center for Complementary and Alternative Medicine

*NCI*

National Cancer Institute

*NDA*

new drug application

*NEI*

neuroendocrine-immune network

*NIH*

National Institutes of Health

*NIR*

near-infrared

*NIRS*

near infrared spectrometer; near infrared spectrometry

*NLM*

National Library of Medicine

*NMR*

nuclear magnetic resonance

*NOAEL*

no-observed-adverse-effect level

*NOE*

nuclear Overhauser effect

*NOESY*

nuclear Overhauser effect spectroscopy

*NP-LC*

normal phase liquid chromatography

*ODS*

octadecasilica

*OHRP*

Office for Human Research Protections

*ORAC*

oxygen radical absorbance capacity

*ORD*

optical rotatory dispersion

*ORR*

objective response rate

*OVX*

ovariectomized rat model

*PB*

particle beam

*PBS*

phosphate buffer saline

*PC*

paper chromatography

*PCR*

polymerase chain reaction

*PD*

pharmacodynamics

*PE*

phosphatidylethanolamine

*PK*

pharmacokinetics

*PLE*

pressurized liquid extraction

*PMS*

phenazine methosulfate

*pQCT*

peripheral quantitative computed tomography

*PQR*

product quality review

*PR*

progesterin receptor

*PRMA*

Pharmaceutical Research and Manufacturers of America

*PTLC*

preparative thin layer chromatography

*QA*

quality assurance

*QC*

quality control

*QOL*

quality-of-life

*QRM*

quality risk management

*QT*

Q wave and T wave in ECG

*QU*

quality unit

*RACE*

rapid amplification of cDNA ends

*RAPD*

random amplified polymorphic DNA

*RDA*

retro-Diels-Alder

*RFLP*

restriction fragment length polymorphism

*RI*

refractive index

*RP-LC*