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Medicinal Plants - Recent Advances in Research and Development

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This book is dedicated to commemorate
the 70th birthday of
Professor Dr. Hsin-Sheng Tsay,
who has made an immense contribution to
the research on medicinal plants in Taiwan
and has trained and mentored thousands
of young minds in the techniques
of plant tissue culture and beyond.

Preface

The editors thought of bringing out this book given the importance of medicinal plants in human health and vigorous ongoing efforts worldwide in the research and development of medicinal plants. The book contains a plethora of information about resources and conservation; biosynthesis and metabolic engineering; biotechnological tools including bioreactor technology; phytochemical research; herbal medicines and plant-derived agents in cancer prevention and therapy, in metabolic syndrome management, and in the modulation of immune-related disorders; and toxicology of medicinal plants. The book consists of 20 chapters, mostly review articles written by experts in their respective fields.

Chapter 1 consists of ten case studies of promising new drug discovery resulting from the Chinese herbal medicine (CHM)-derived products. In each case study, the active principles of CHM have been elucidated. Chapter 2 describes the ethnopharmacological role of *Scutellaria lateriflora* and its medicinal applications in detail. Also, it contains a summary of the mechanism of action attributed to the neuroprotection and other pharmacological actions associated with *S. lateriflora*. Chapter 3 provides an overview of drug adulteration and evaluation of herbal products with a special reference to the approaches in adulterant detection and regulatory perspectives to control such malpractices. Also, adulteration in slimming phytotherapeutic formulations and PDE-5 inhibitors in herbal formulations have been discussed. Chapter 4 contains an overview of the application and challenges and success of various candidate markers used in the DNA barcoding of plants. The development of multilocus and tiered approaches along with the new frontier areas for application of DNA barcoding of medicinal plants and its products has been analyzed in detail. Chapter 5 summarizes the current development in "omics" approaches in the investigation of selected pharmacologically bioactive compounds from three major classes of secondary metabolites, terpenoids, alkaloids, and phenolics, which are being used as drugs in the prevention or therapy of human diseases. Chapter 6 describes the research findings on in vitro plant regeneration, genetic transformation, and molecular characterization of some of the genes involved in the bacoside biosynthesis in the memory booster plant *Bacopa monniera* (Brahmi). Chapter 7 pertains to the metabolic engineering of isoprenoid pathway using squalene synthase

as a tool to enhance secondary metabolite contents in *Withania somnifera* (Ashwagandha) or commonly known as Indian ginseng. Chapter 8 reviews the reports on in vitro methodologies, the use of different elicitors, gene functions, genetic modifications, and expression profiling for a better understanding of and to enhance the constituents in *Salvia miltiorrhiza*. Chapter 9 reviews the work carried out on in vitro propagation, somatic embryogenesis, and controlling hyperhydricity (vitrification) in cultures of selected medicinal plant species in Taiwan. Chapter 10 describes the commercial production of paclitaxel, 10-deacetylbaccatin III (10-DAB), and camptothecin (CPT) by the cultivation of plants by farming and production of raw materials and target compounds by cell or hairy root cultures in bioreactors. Chapter 11 provides comprehensive information on the biological effects and pharmacological importance of lucidone, an active constituent of fruits and leaves of *Lindera erythrocarpa*. Chapter 12 briefly describes various aspects of pharmacokinetics, which need to be addressed to generate reliable data on safety and efficacy of herbal drugs. Chapter 13 reviews the role of green tea in cancer prevention and therapy. Chapter 14 presents a review on the traditional Chinese medicine (TCM) oncology theory and its approach toward cancer, therapeutic effects, and various anticancer compounds obtained from TCM herbal plants with the hope of providing a better understanding of the role of drugs in the treatment of cancer. Chapter 15 outlines the results of various scientific studies on *Angelica* species that were reported to have anticancer and antitumor activities. Chapter 16 illustrates the clinical utilization of Chinese herbal medicines acting on rheumatoid arthritis (RA), elucidates their mechanism of action, analyses their limitations and problems, and discusses their development and application prospects. Chapter 17 describes the status, health sector responses, role of traditional medical practitioners, medicinal plant use, and its challenges in the management of noncommunicable diseases in Uganda. Chapter 18 explores possible immune molecular targets of disease-modifying antirheumatic herbal agents and discusses their role in the management of arthritic conditions. Chapter 19 describes the causes and pathophysiology of diabetes, its perspective in Ayurveda, and Ayurvedic plants having antidiabetic potential. Finally, Chapter 20 presents a brief overview of the mechanism of hepatotoxicity and highlights the nexus between herbal medicines and liver injury. Also, it discusses the potential ways that can assure quality check of herbal medicines through the imposition of regulatory laws, databases, and resorting to toxicogenomics.

The editors hope that this compendium of review articles will be very useful as a reference book for advanced students, researchers, academics, business houses, and all people concerned with medicinal plants.

Taichung, Taiwan — Hsin-Sheng Tsay
Taipei, Taiwan — Lie-Fen Shyur
Taichung, Taiwan — Dinesh Chandra Agrawal
May 2016 — Yang-Chang Wu
Sheng-Yang Wang

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The editors wish to place on record special thanks to one of the editors of this book Professor Agrawal for initiating the book, handling the correspondence, and managing it from the start to finish. Without his untiring efforts, this book would not have seen the light of the day.

The editors sincerely thank Springer for publishing this book and all the Springer staff members who were ever ready to answer our queries about the book. We would especially like to place on record our appreciation and thanks to Ms. Aakanksha Tyagi, who from the day one handled the correspondence very efficiently and provided all needed help to make this book a reality.

Peer reviewing is an important component of technical writing. The editors would like to express their sincere thanks to all the peer reviewers who took time out from their busy schedules and provided their critical comments on several manuscripts. It helped us to maintain a certain standard of the chapters. We would especially like to thank Professor Dhanasekaran of the Department of Drug Discovery and Development, Harrison School of Pharmacy, Auburn University, Auburn, USA; Dr. Neha Patel, Division of Plant Sciences, Research School of Biology, College of Medicine, Biology and Environment, the Australian National University, Canberra ACT 0200, Australia; Dr. Sushim Gupta, Bacterial Epidemiology and Antimicrobial Resistance Research Unit, USDA, ARS, Athens, GA, USA; Dr. Rishi Kishore Vishwakarma, Le CBS-Centre de Biochimie Structurale-CNRS, UMR 5048-UM-INSERM U 105429 rue de Navacelles 34090, Montpellier, France; Dr. Manish Nivsarkar, Director, Department of Pharmacology and Toxicology, BV Patel Pharmaceutical Education and Research Development (PERD) Centre, Ahmedabad, India; and Dr. Pathirage Kamal Perera, Institute of Indigenous Medicine, University of Colombo, Rajagiriya, Sri Lanka, for their help in peer reviewing some of the manuscripts.

One of the editors, Professor Agrawal, wishes to thank his spouse Mrs. Manju Agrawal for being a great support throughout the book and never complained about his working at home at late hours and weekends. Also, he wishes to thank his daughters Ms. Somya and Ms. Neha for their help in proofreading some of the manuscripts.

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About the Editors and Contributors

About the Editors

Hsin-Sheng Tsay, Ph.D. Professor/Dr. Hsin-Sheng Tsay is a renowned researcher and teacher. He completed his Ph.D. in agronomy from the National Taiwan University about 40 years ago. He worked with Professor Toshio Murashige, University of California, Riverside, for his Ph.D. on anther culture of tobacco. Later, he served at the Taiwan Agricultural Research Institute (TARI) for about 25 years and became head of the Agronomy Department. In TARI, his research pertained to anther culture of rice. There, he also worked on asparagus, papaya, sweet potato, and bamboo. For the last 25 years, Prof. Tsay has been working with medicinal plants indigenous to Taiwan and China. For the last 14 years, he has been working at the Chaoyang University of Technology. There he served as dean of the College of Science and Engineering and director and chair professor of the Graduate Institute of Biotechnology. Professor Tsay has transferred about 20 technologies pertaining to the functional foods for commercialization. He has published 265 research papers and has guided 23 Ph.D. and more than 100 master's students.

Professor Tsay has made a significant contribution to the biotechnology of medicinal plants. During his career, he has organized about 80 plant tissue culture training workshops for international and national researchers. Of these, about 45 tissue culture workshops were conducted for local researchers, professors, vocational school teachers, students, and farmers. These were sponsored by the National Science Council and the Council of Agriculture, Taiwan. About 35 workshops were supported by the International Cooperation and Development Fund (ICDF), and the National Science Council, Taiwan. Participants (more than 500) in these workshops came from about 40 countries. Professor Tsay was invited by 13 countries to conduct plant tissue culture training workshops. He has a galaxy of students across the globe.

During his career, Prof. Tsay has won several national and international awards, including the "National Science Council Outstanding Research Award" for three times. He is on the editorial boards of several international journals and serves as a reviewer for several SCI journals of plant biotechnology.

Lie-Fen Shyur, Ph.D. Professor/Dr. Lie-Fen Shyur is currently serving as a research fellow and deputy director in the Agricultural Biotechnology Research Center, Academia Sinica, Taiwan, and also holding adjunct or joint professorships at five academic institutions in Taiwan. She has participated as editorial board member and invited referee for many international scientific journals and governmental and academic committees.

Dr. Shyur's lab research foci include (1) research and development of phytomedicines and their derived phyto-agents for prevention or therapy of inflammatory diseases, including cancers, septic shock, and hepatitis, (2) elucidating biosynthesis pathway of pharmacologically bioactive compounds in medicinal plants, and (3) industrial enzyme biotechnology. Her research achievements include publication of lab results in high-caliber and reputed journals, such as *Pharmacology and Therapeutics*, *Cancer Research*, *Molecular and Cancer Therapeutics*, *Molecular Oncology*, *Current Opinion in Chemical Biology*, *Molecular Medicine*, *Journal of Biological Chemistry*, *Environmental Science &Technology*, *Journal of Medicinal Chemistry*, and others. In addition, Dr. Shyur has obtained more than 25 international patents and two national awards, namely, the 2014 Silver Award of the National Invention and Creation and the 10th National Innovation Award (2013). A few of technology licensing and cooperative research and development agreement (CRADA) and projects were/are proceeded with local biotech or pharmaceutical companies. The ultimate goal of Dr. Shyur's lab research is to develop agricultural or plant-derived agents for human health-care or bio-industrial applications.

Dinesh Chandra Agrawal, Ph.D. Professor/Dr. Agrawal graduated in 1976 from the Aligarh Muslim University (Central Govt. University) and after that obtained his Ph.D. degree in 1982 from the Garhwal University (renamed as Hemwati Nandan Bahuguna Garhwal University and became Central Govt. University since 2009). His Ph.D. research work on the physiological aspects of *Pinus caribaea* was carried out at the Forest Research Institute, Dehradun (Central Govt. Institute). After his Ph.D. degree, Professor Agrawal has more than 34 years of research experience in plant biotechnology of diverse species including medicinal plants. After serving for more than 31 years, in 2013, he retired as a chief scientist and professor of biological sciences from the CSIR-National Chemical Laboratory, Pune, the top ranking institute in chemical sciences under the umbrella

of Council of Scientific and Industrial Research (CSIR), Ministry of Science and Technology, Govt. of India. Currently, he is working as a professor in the Department of Applied Chemistry, Chaoyang University of Technology (CYUT), Taiwan.

While in CSIR-NCL, Professor Agrawal worked as a coordinator and project leader of several research projects funded by the Govt. of India. He has more than 155 research articles to his credit on different aspects of plant biotechnology including medicinal plants. Also, he has written two books on "laboratory record writing." More than 35 M.Tech./M.Sc. and 7 Ph.D. students have completed their thesis work under his guidance.

Professor Agrawal has been bestowed several prestigious awards and fellowships such as the Alexander von Humboldt Fellowship (Germany), DBT Overseas Associateship (USA), British Council Scholar (UK), European Research Fellow (UK), and INSA Visiting Scientist. During these fellowships, he had opportunities to work in the USA, Germany, and the UK. Also, he had research collaboration with UMR Vigne et Vins, INRA, Centre de Recherché Colmar, France.

Professor Agrawal has served as a member of the editorial board of *Medicinal and Aromatic Plant Abstracts*, NISCAIR, Govt. of India, and has reviewed a large number of research papers for several SCI journals on plant biotechnology. For more than 10 years, he has been a member of the executive committee of the Humboldt Academy, Pune Chapter, and held the position of treasurer.

Yang-Chang Wu, Ph.D. Professor/Dr. Yang-Chang Wu was born in Chiayi, Taiwan, in 1951. He obtained his Ph.D. in pharmacognosy from the College of Pharmacy, Kaohsiung Medical University (KMU), Taiwan, in 1986. After that, he joined the group of Prof. Yoshimasa Hirata at Meijo University, Japan, as a postdoctoral researcher from 1986 to 1987. Later, he joined the laboratory of Prof. Kuo-Hsiung Lee for further postdoctoral research at the University of North Carolina (UNC), Chapel Hill, USA. There he worked on the various synthetic approaches toward natural products and medicinal chemistry.

In 1990, he became professor at the College of Pharmacy at KMU and director of the Graduate Institute of Natural Products (GINP) in 1992. Later, he served as the dean of the Office of Research and Development at KMU, from 2006 to 2009. Attributed to his significant contribution to research on natural products, he was selected as the chair professor and vice-president of the Graduate Institute of Integrated Medicine and College of Chinese Medicine at China Medical University (CMU), Taiwan, from 2010 to 2012. Since 2012, he was appointed as the chair professor and vice-president as well as dean of the School of Pharmacy, CMU, Taiwan.

In 2007, he was awarded by the Wang Ming-Ning Foundation for outstanding merit and high scholastic achievement to medical and pharmaceutical research. In 2009, he received the National Science Council Outstanding Research Award in Taiwan. He also received the Outstanding Medical and Pharmaceutical Technology

Award in 2010 by the TienTe Lee Biomedical Foundation, Taiwan. Professor Wu is known for his expertise in the area of translational research on Chinese herbal medicine, functional food, and new drug development.

Professor Wu has served as an editorial board member of 6 journals and as a referee for about 30 journals. Also, he is an outstanding member of the American Society of Pharmacognosy (ASP) and ten more other associations. So far, Prof. Wu has published more than 510 research articles in SCI journals along with the authorship in several book chapters. He has been granted more than 30 patents and is in cooperation with more than 20 industry-academic organizations. Professor Wu has transferred six patent/technologies (including one new drug R&D tech transfer) to industry.

Sheng-Yang Wang, Ph.D. Dr. Sheng-Yang Wang is a distinguished professor at the Department of Forestry, National Chung Hsing University, Taiwan. Dr. Wang obtained his Ph.D. degree from the National Taiwan University. He is one of the well-known phytochemists in Taiwan and has expertise in the qualitative and quantitative determination of natural products by chromatography and spectroscopy. He has published more than 120 scientific articles so far. Dr. Wang has obtained several important scientific awards in his academic career, including "Excellent Research Award" for Young Faculty of National Chung Hsing University (2004); Dr. Ta-You Wu Memorial Award established by the National Science Council (2004), Taiwan; Academia Award of the Chinese Forestry Association and Top 10 Outstanding Agricultural Specialists of Taiwan in 2011; Academic Award, Forest Products Association of ROC; Academician Shang-Fa Academy Award for Distinguished Young Scholars in 2012; Development Program of Industrialization for Agricultural Biotechnology (DPIAB) Award for Outstanding Industry-University Collaboration Projects in 2013; Silver Award of the National Invention and Creation 2014; and Gold Award in "Seoul International Invention Fair 2014." The research areas of interest in Dr. Wang's laboratory are (1) development of new methodology in the isolation and structural elucidation of natural products, (2) phytomedicine investment of indigenous plants of Taiwan, and (3) functional genomic study of woody plants.

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Chapter 1
Chinese Herbal Medicine-Derived Products for Prevention or Treatment of Diseases Affecting Quality of Life

Kuo-Hsiung Lee, Susan L. Morris-Natschke, Yu Zhao, and Katie Musgrove

Abstract Chinese herbal medicine (CHM) has been used for several thousands of years to treat human illness, which makes CHM the best source to provide valuable and unique information for modern drug discovery and development. Development of CHM products as adjunct therapies to augment the efficacy and offset the toxicity of Western medicine is an excellent approach for rapid advancement into US FDA-approved new drugs. Developing CHM products as high-quality dietary supplements must particularly emphasize standardization through qualitative and quantitative quality controls on single herbs and multiple herbs of the prescription formulas by using the most advanced scientific technology, especially toxicity profile testing. A combination of advanced medicinal chemistry and natural products chemistry, coupled with cutting-edge life science technology, will play a very important role for converting CHM products, especially the pure single active principles, through modification and synthesis into clinical trial candidates very efficiently and effectively. This chapter presents ten case studies of promising new drug discovery resulting from CHM-derived products: compounds from *Curcuma longa* (Jiang Huang), *Antrodia camphorata* (Chang-ku), *Apium graveolens* (Han Qin), *Momordica charantia* (Ku Gua), *Monascus purpureus* (Hong Chi), *Astragalus membranaceus* (Huang Chi), *Scutellaria* decoction (Huang Chin Tang), *Eucommia ulmoides* (Tu Chung), *Ligusticum wallichii* (Chuan Chiung), and *Lycium barbarum* (Kou Chi Tzu).

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Keywords Chinese herbal medicine (CHM) • Drug discovery and development • Disease prevention and treatment • Medicinal chemistry • Natural products chemistry • Traditional Chinese medicine (TCM)

Abbreviations

Ach	Acetylcholine
AIDS	Acquired immunodeficiency syndrome
ANS	1-anilino-8-naphthalene-sulfonate
ATP	Adenosine triphosphate
BDFI	Bioactivity-directed fractionation and isolation
CD	Circular dichroism
CHM	Chinese herbal medicine
COX	Cyclooxygenase
CRF	Cancer-related fatigue
DNA	Deoxyribonucleic acid
EDHF	Endothelium-derived hyperpolarizing factor
EGFR-TKI	Epidermal growth factor receptor tyrosine kinase inhibitor
FDA	Food and Drug Administration
FRET	Förster-type fluorescence resonance energy transfer
FTIR	Fourier transform infrared spectroscopy
GAP	Good agriculture practice
GCP	Good clinical practice
GI	Gastrointestinal
GLP	Good laboratory practice
GMP	Good manufacturing practice
GRAS	Generally recognized as safe
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HIV-1	Human immunodeficiency virus type 1
HPLC	High-pressure liquid chromatography
HPV	Human papilloma virus
IC_{50}	Half maximal inhibitory concentration
IL	Interleukin
IND	Investigational New Drug
iNOS	Inducible nitric oxide synthase
IOIP	Idiopathic orbital inflammatory pseudotumors
IV	Intravenous
LBP	*Lycium barbarum* polysaccharide
MALDI-TOF MS	Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry
*mc*IRBP	*Momordica charantia* insulin receptor (IR)-binding protein

MCP	Monocyte chemoattractant protein
MOEA	Ministry of Economic Affairs
NBP	3-*n*-butylphthalide
NOS	Nitric oxide synthase
RCT	Randomized controlled trial
RMR	Red mold rice
SFDA	State Food and Drug Administration
TCM	Traditional Chinese medicine
TNF	Tumor necrosis factor
US	United States
WHO	World Health Organization

1.1 Introduction

Generations of Chinese people have used Chinese herbal medicine (CHM), the most important medicine of traditional Chinese medicine (TCM), for thousands of years for disease prevention and treatment. CHM and their active principles and derivatives provide a broad and profound base for the discovery of effective and safe dietary supplements, in addition to new medicine for the prevention or treatment of diseases affecting quality of life. The symbiotic relationship between the ancient practice of CHM, with its thousands of years of experience, and the modern technology and scientific advancements of today has proven to be the key to effective new drug discovery and development.

The knowledge base of CHM is both vast and diverse. Chinese medicines are all derived from natural products, with roughly 90 % coming from plants. Approximately 5000 plant species with therapeutic value have been identified, many of them used as *Min Chien Yao*, or folk drugs. About 500 of them are commonly prescribed by doctors of Chinese medicine based on a series of systemic and self-contained theories (Chung Yao, *Chinese Materia Medica*). This systematic approach is necessary because most CHM-derived products involve multicomponent processed herbal formulations. Although CHM does not provide the same scale and scope of modern-day clinical trials, they no doubt offer a vast knowledge base from which to gain valuable insights relevant to current chronic health issues. The combination of CHM and modern scientific practices has the potential to lead to both new clinical trial candidates and adjunct therapies for current Western medicine treatments (Lee et al. 2013).

In 2013, the authors detailed several case studies of modern drug discovery from CHM, including ephedrine/pseudoephedrine from *Ephedra sinica* (Ma Huang), indirubin from *Indigofera tinctoria* (Qing Dai – Dang Gui Long Hui Wan), and artemisinin from *Artemisia annua* (Qing Hao) (Lee et al. 2013). It should be noted that Tu Youyou from the China Academy of Chinese Medical Sciences, Beijing, was recognized in 2011 with the Lasker-DeBakey Clinical Medical Research Award

and in 2015 together with Drs. Satoshi Ōmura and William C. Campbell, with the Nobel Prize in Physiology or Medicine, based on her outstanding contribution for the discovery of artemisinin in malaria therapy. Tu Youyou is credited with the inspiration and diligence to probe the ancient CHM literature for an applicable solution to malaria, which ultimately led to the identification of artemisinin/qinghaosu as the effective active principle. Dr. Yi Zhao of Guangxi Traditional Chinese Medical University, China, also made a significant contribution with regard to the elucidation of the pharmacological effect, as well as the mechanism of action of artemisinin/qinghaosu as evidenced in his academic papers entitled *Studies on Artemisia annua L./Qinghaosu* (Zhao et al. 1986, 1987; Zhao 2011). Overall, the discovery of artemisinin serves as the best example of producing a world-class new drug from ancient CHM via modern medicinal chemistry studies.

1.1.1 Current Areas of Interest for CHM-Derived Drugs

Chronic diseases such as diabetes, arthritis, heart disease, high blood pressure, etc. can be debilitating to patients and can drastically alter their quality of life. CHM has the potential to offer solutions to many of these modern chronic diseases. Some of the current areas of interest for scientists focusing on CHM-derived drug discovery are as follows: antioxidant and antiaging activity, blood pressure-lowering effects, hypolipidemic action, blood sugar-lowering effects, antiallergic functions, and anti-arthritis properties. While we highlight quite a few CHM-derived drugs in our case studies, there are other notable discoveries concerning the treatment and prevention of these devastating chronic diseases.

In the coming years, CHM will lead to many new clinical trial drug candidates. The ancient practices of CHM combined with modern scientific evidence have clearly demonstrated that CHM can be a promising treatment modality for chronic diseases to greatly improve quality of life for patients. This combination of ancient and modern-day principles may also lead to a higher probability of success and a more efficient scientific process. This chapter presents ten case studies of promising new drug discovery resulting from CHM-derived products: compounds from *Curcuma longa* (Jiang Huang), *Antrodia camphorata* (Chang-ku), *Apium graveolens* (Han Qin), *Momordica charantia* (Ku Gua), *Monascus purpureus* (Hong Chi), *Astragalus membranaceus* (Huang Chi), *Scutellaria* decoction (Huang Chin Tang), *Eucommia ulmoides* (Tu Chung), *Ligusticum wallichii* (Chuan Chiung), and *Lycium barbarum* (Kou Chi Tzu).

1.2 Bringing TCM to Mainstream

1.2.1 Obstacles for Bringing TCM to Mainstream

Lack of standardization is a major obstacle to the development of CHM as world-class dietary supplements and new medicines. Unless herbal products can be guaranteed to be efficacious and safe with validated quality and consistency, they cannot be patented or tested in clinical trials. Even their commercialization and marketing as dietary supplements are weakened without such assurances. Four issues to be addressed in bringing CHM products into the mainstream pharmaceutical market are as follows: *high quality*, *high consistency*, *high safety*, and *high efficacy*. Good methods of quality control should be applied at all stages, including plant growth, production, processing, and storage. In addition, the products should be validated as being from the correct plant species, plant strain, and plant part as well as uniform from manufacturer to manufacturer and from batch to batch. The products must be free of toxicity and contaminants (e.g., heavy metals) with all of their constituents characterized. Possible interactions with other drugs must be determined, and controlled clinical trials should be performed to prove efficacy.

1.2.2 Methods for Bringing TCM to Mainstream

Two main areas for development of CHM products are as adjunct therapies to Western medicine and for prevention or treatment of diseases that are difficult to be treated satisfactorily with Western medicine. Strategies for development of CHM-based world-class new drugs should emphasize using *medicinal chemistry approaches* to study the active principals of CHM and to modify the lead compound into suitable clinical trial candidates. Furthermore, *mechanism of action studies* on active principles, active extracts, and effective formulas of CHM can provide needed scientific proof and future directions for new drug research. Also, it would be extremely helpful to establish *international collaborative platforms* for development of CHM-based new drugs.

Two examples of new botanical drugs already approved by the US FDA are Veregen (MediGene, Germany) in October 2006 and Fulyzaq (Salix Pharmaceuticals, USA) in December 2012. These products were indicated for use against human papilloma virus (HPV) and noninfectious diarrhea in adult patients with HIV/AIDS on antiretroviral therapy, respectively. Their major constituents are kunecatechins (component mixture from a green tea extract) and crofelemer (an extract from *Croton lechleri*), respectively.

A national program for developing world-class new botanical drugs was initiated by the Ministry of Economic Affairs (MOEA), Taiwan, during 2000–2005 (Lee 2015). The seven-person committee (Committee for Promotion of Chinese Herbal Medicine Industry and Technology) received FDA approval for four Investigational

New Drug (IND) applications for partially purified Chinese herbal medicine products for clinical trials, established a platform technology to produce high-quality herbal medicine products with cutting-edge methodology for quality control, and founded excellent preclinical and IND-related infrastructures, including good agriculture, laboratory, manufacturing, and clinical practice (GAP, GLP, GMP, and GCP). Both the software and hardware of these infrastructures were set up to international standards (Lee 2015).

Medicinal chemistry is the art of combining *chemistry* and *biology* for optimal drug discovery, and these two research areas are complementary, just like *yin* and *yang* of TCM. The discovery of new bioactive compounds depends on valid biological assays, and new chemistry can make the discovery of new biological targets possible.

CHM-derived world-class new drugs and high-quality dietary prescriptions can come from three sources: herbal formulas, extract fractions, and single herbs. As mentioned above, the quality control of herbal formulas is critical, while any modification and improvement should be followed by reevaluation of efficacy and toxicity. In all cases, herbal formulas should continue to be used according to the conformation dictated by TCM diagnosis and principles. Both herbal formulas and single herbs from those formulas can be subjected to pharmacological testing as well as bioactivity-directed fractionation and isolation (BDFI) to discover active fraction mixtures and active single natural product lead compounds, respectively. After the structures of the active lead compounds are elucidated, an optimized lead can be pursued through an iterative cycle that includes the design of modified analogs, synthesis of these analogs, bioactivity screening, and analysis of results. Various preclinical studies to discern mechanism of action and other pharmacological properties (solubility, pharmacokinetics, etc.) are important to make sure that a lead is a viable clinical trial candidate. The goals of the lead development process are to improve pharmacological profiles by increasing activity, decreasing toxicity, or circumventing metabolic, pharmacokinetic, solubility, or drug-resistance problems. The following case studies will highlight the rationale, diversity, and strength of these processes as well as introduce several examples of CHM-derived drugs used now or in the future to treat or prevent diseases affecting quality of life.

1.3 Case Studies Highlighting CHM-Derived Drugs Used to Treat/Prevent Diseases Affecting Quality of Life

1.3.1 Curcuma longa *(Turmeric)*

1.3.1.1 Introduction

Curcuma longa (Chinese: Jiang Huang 薑黃) is a rhizomatous herbaceous perennial member of the Zingiberaceae family. More commonly known as turmeric, it is native to tropical Southeast Asia and now cultivated in the tropical and subtropical

regions of the world, especially in India and China. Turmeric has a long historical use as a traditional medicine. In Ayurveda medicine, turmeric is primarily used as a treatment for inflammatory conditions. In TCM, it is used to treat biliary disorders, anorexia, cough, diabetes, wounds, hepatic disorders, and rheumatism. It has also been used as a sinusitis stimulant, aspirant, carminative, emmenagogue, astringent, detergent, and diuretic (Gupta et al. 2015). Besides its medicinal use, turmeric has long been part of the daily diet in Asian countries and has not been shown to cause any toxicity. Turmeric powder and many other extracts from the rhizomes were found to possess versatile bioactivity, including wound-healing, anti-inflammatory, hypolipidemic, cytotoxicity, antiprotozoan, antibacterial, antifungal, and antifertility effects (Chattopadhyay et al. 2004).

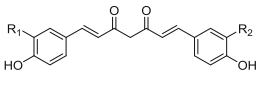
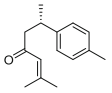
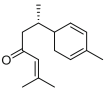
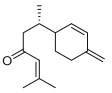
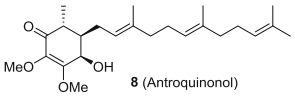
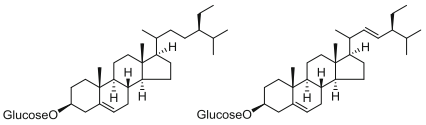
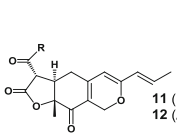
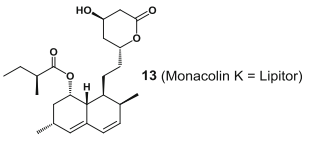
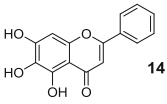
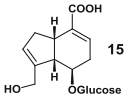
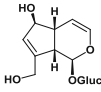
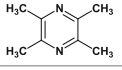
1.3.1.2 Chemical Constituents

To date, over 200 compounds have been identified from turmeric. These compounds belong to various structural types including diarylheptanoids (curcuminoids), diarylpentanoids, phenylpropene, phenolic compounds, monoterpenes, sesquiterpenes, diterpenes, triterpenoids, alkaloid, sterols, and fatty acids (Anonymous 1999b).

Curcuminoids with an aryl-C7-aryl skeleton, include curcumin (curcumin I, **1**, Table 1.1), demethoxycurcumin (curcumin II, **2**, Table 1.1), bisdemethoxycurcumin (curcumin III, **3**, Table 1.1), *p*,*p*′-dihydroxydicinnamoyl methane, *p*-hydroxycinnamoyl-feruloylmethane, dihydrocurcumin, etc. Sesquiterpenes include *ar*-turmerone (**4**, Table 1.1), a-turmerone (**5**, Table 1.1), β-turmerone (**6**, Table 1.1), curlone, etc. Dried turmeric rhizomes usually contain 1.5–5 % essential oils. Compounds **4**–**6** are the major sesquiterpenes of the essential oils, and these compounds may account for at least 40 % of essential oils of turmeric rhizomes.

The pharmaceutical products of turmeric are dried whole rhizomes, ground turmeric, turmeric oils, turmeric oleoresin, and curcumin. The quality control of turmeric has been thoroughly reviewed (Li et al. 2011). Curcuminoids are the main active compounds. They are primarily accumulated in turmeric rhizomes (3–15 %) with curcumin (**1**, Table 1.1) as the principal constituent. The contents of curcuminoids in turmeric rhizomes often vary with varieties, locations, sources, and cultivation conditions. According to the Indian Pharmacopoeia in 1996, dried turmeric rhizomes should contain not less than 1.5 % of curcumin (**1**) (w/w) (India 1996). The Pharmacopoeia of the People's Republic of China (2005) requires no less than 1.0 % of curcumin (**1**) content (w/w) in dried turmeric rhizomes (Anonymous 2005). The Thai Herbal Pharmacopoeia recommended that dried turmeric should contain no less than 6 % of turmeric oil (v/w) and 5 % of total curcuminoids (w/w) (Thaikert and Paisooksantivatana 2009). The WHO (World Health Organization) suggests that not less than 4.0 % of volatile oil, and not less than 3.0 % of curcuminoids should be present in turmeric (Anonymous 1999d). The quality control of rhizomes, powders, and extract products was reported through defining and verifying the presence of curcumin (**1**), demethoxycurcumin (**2**), and bisdemethoxycurcumin (**3**) and determining their concentrations by HPLC chromatogram (Li et al.

Table 1.1 Structures of selected bioactive compounds from plant species in the case studies

Case study	Natural species	Examples of active compounds or modified derivatives
1	*Curcuma longa*	 **1** (Curcumin) $R_1 = OCH_3$, $R_2 = OCH_3$ **2** (Demethoxycurcumin) $R_1 = OCH_3$, $R_2 = H$ **3** (Bisdemethoxycurcum) $R_1 = H$, $R_2 = H$ **7** (JC-9 = ASC-J9) $R_1 = OCH_3$, $R_2 = CH_3$  **4** (*ar*-Turmerone)  **5** (α-Turmerone)  **6** (β-Turmerone)
2	*Antrodia camphorata*	 **8** (Antroquinonol)
3	*Apium graveolens*	 **9** (*S*-(-)-3-*n*-Butylphthalide, *S*-(-)-NBP)
4	*Momordica charantia*	 **10** (Charantin: mixture of sitosteryl glucoside (left) & stigmasteryl glucoside (right))
5	*Monascus purpureus*	 **11** (Monascin) R = C_5H_{11} **12** (Ankaflavin) R = C_7H_{15}  **13** (Monacolin K = Lipitor)
6	*Astragalus membranaceus*	Immunostimulating polysaccharides
7	*Scutellaria baicalensis* (one of four herbs in Huang Chin Tang	 **14** (Baicalein)
8	*Eucommia ulmoides*	 **15** (Geniposidic acid)  **16** (Aucubin)
9	*Ligusticum wallichii*	 **17** (Tetramethylpyrazine = ligustrazine = chuanxiongzine)
10	*Lycium barbarum*	*Lycium barbarum* polysaccharides (LBPs)

2011). Turmeric oils and oleoresins with various promising activities have been marketed globally. To control the quality of these products, Ar-turmerone (**5**), turmerone (**6**), and β-turmerone (**7**) are usually employed as chemical markers, for example, a minimum of 40 % of these compounds in turmeric oils and oleoresins are required (Li et al. 2011).

1.3.1.3 Bioactivity

The primary active compound of turmeric is curcumin (**1**, Table 1.1), which is also responsible for turmeric's vibrant yellow color. Curcumin was isolated in 1815, obtained in crystalline form in 1870, and ultimately identified as 1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione-(1E,6E) (Miłobdzka and Lampe 1910). Chemically, curcumin is a diarylheptanoid, in which two ferulic acid fragments are connected by a methylene bridge. The β-diketone moiety of curcumin can undergo keto–enol tautomerism (Fig. 1.1) and exists entirely in the enol form in both solution and solid phases (Pedersen et al. 1985).

Extensive studies have indicated that curcumin possesses versatile bioactivity, including anticarcinogenic, immunomodulatory, antioxidant, anti-inflammatory, anti-angiogenesis, anticancer, chemopreventive, anti-Alzheimer's disease, antithrombotic, antimalarial, anti-rheumatoid arthritis, anti-HIV, wound healing, antihepatotoxic, anti-psoriasis, hypoglycemic, and antihyperlipidemic effects. Thus, curcumin has therapeutic potential against a wide range of diseases, such as

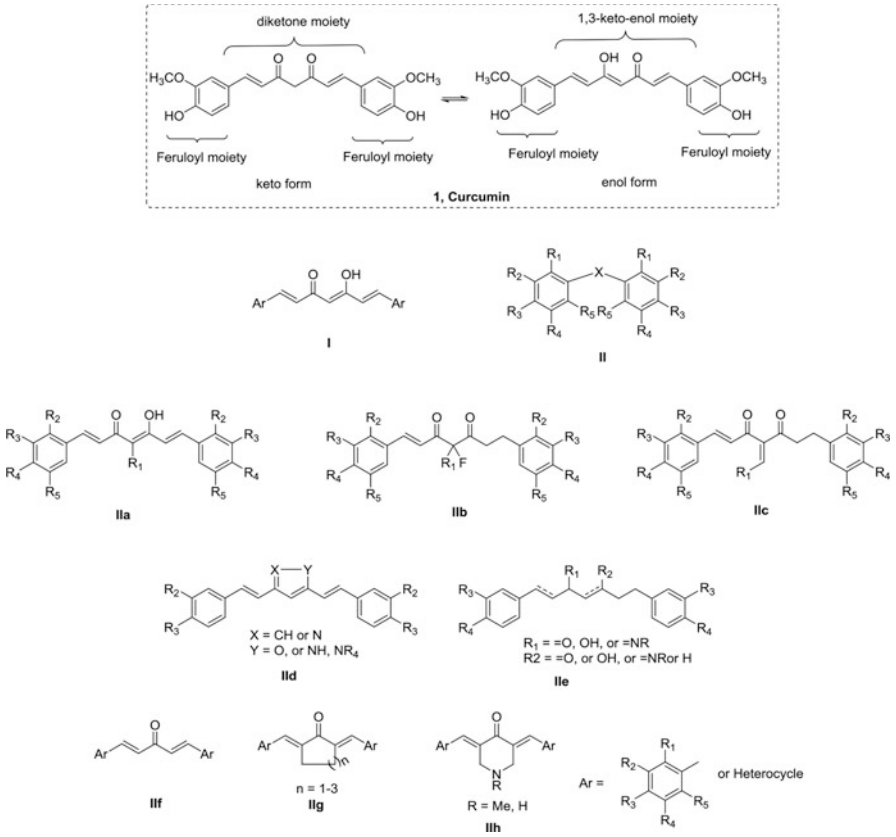


Fig. 1.1 Tautomerism of curcumin and design of different analogs