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

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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).

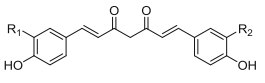
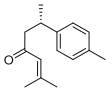
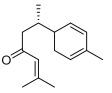
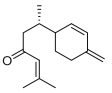
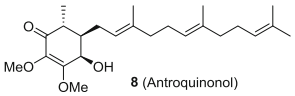
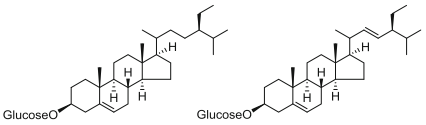
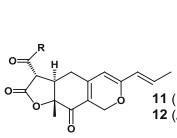
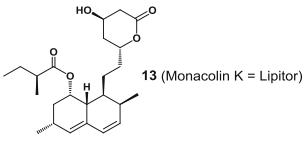
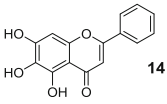
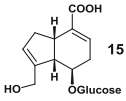
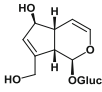
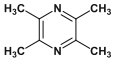
1.3.1.2 Chemical Constituents

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

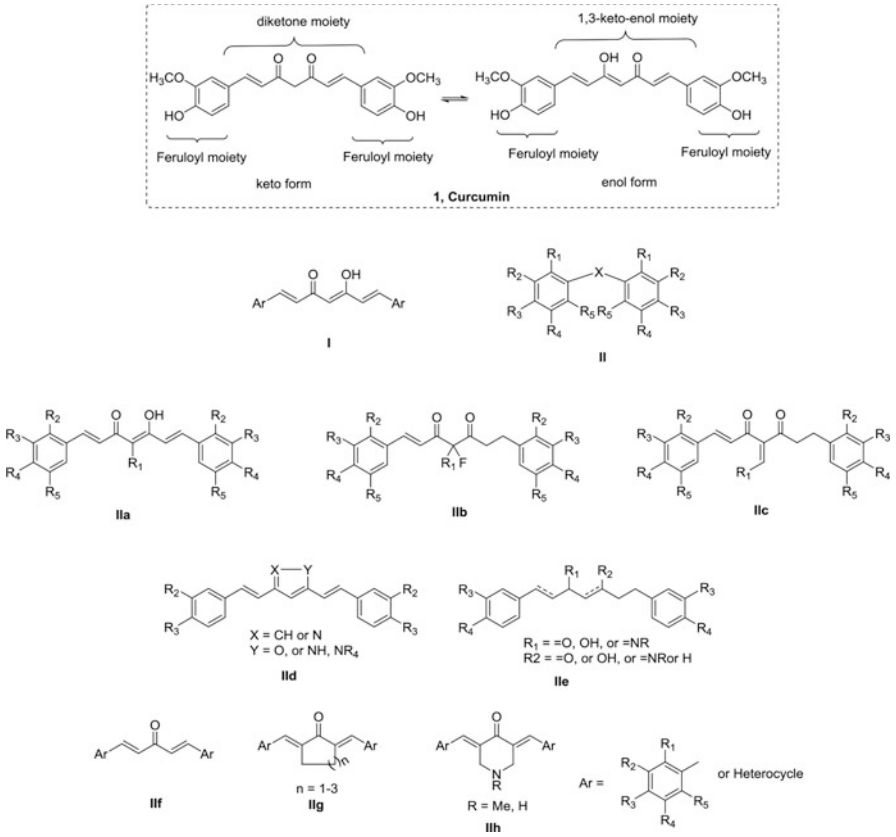


Fig. 1.1 Tautomerism of curcumin and design of different analogs

inflammatory, lung, neurological, liver, metabolic, autoimmune, and cardiovascular diseases, as well as cancers. Nowadays, around 65 clinical trials are ongoing using curcumin for various diseases, especially for anti-inflammatory, chemoprevention, or cancer therapy (Bairwa et al. 2014; Goel et al. 2008; Hsu and Cheng 2007).

Curcumin has been testified to be nontoxic even at high dosages. To date, no toxicity has been found in any animal and human studies of curcumin. It has been classified as "generally recognized as safe" (GRAS) by the National Cancer Institute (Anand et al. 2007; Sharma et al. 2001). However, several pharmacokinetic and pharmacodynamic studies on curcumin have indicated that it is rapidly metabolized, conjugated in the liver, and excreted in the feces, thus having limited systemic bioavailability (Cheng et al. 2000; Ireson et al. 2001). Research studies have shown that the administration doses as high as 8 g of curcumin per day to human subjects resulted in only an average peak serum concentration of ~1.77 μM of curcumin (Anand et al. 2007; Sharma et al. 2001).

1.3.1.3.1 Curcumin Is a Multi-target Natural Compound

Curcumin's versatile activities come from its ability to influence multiple signaling molecules. Numerous studies have shown that curcumin can bind directly to many signaling molecules, enzymes, protein kinases, protein reductases, carrier proteins, metal ions, etc. Various biophysical tools were employed to study interactions of curcumin with its targets. These tools are spectrophotometry, Fourier transform infrared (FTIR), circular dichroism (CD) spectroscopy, fluorescence quenching, Förster-type fluorescence resonance energy transfer (FRET), surface plasmon resonance, competitive ligand binding, radiolabeling, site-directed mutagenesis, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS), immunoprecipitation, phage display biopanning, electron microscopy, 1-anilino-8-naphthalene-sulfonate (ANS) displacement, and co-localization techniques. Moreover, most of these studies have utilized molecular docking as a computational tool to study the mode and site of binding (Gupta et al. 2011).

Curcumin's direct targets on signaling molecules and the different forces that bind the curcumin–protein complex have been well reviewed (Gupta et al. 2011). According to this review, the targets of curcumin fall into the following groups:

1. *Inflammatory molecules*: tumor necrosis factor (TNF)-α, cyclooxygenase (COX)-1, COX-2, human a1-acid glycoprotein (AGP), and myeloid differentiation protein 2 (MD-2);
2. *Enzymes*: histone acetyltransferases, histone deacetylases, glyoxalase I, xanthine oxidase, proteasomes, sarco (endo)plasmic reticulum Ca^{2+} ATPase, human immunodeficiency virus type 1 (HIV-1) integrase and HIV-1 protease, DNA methyltransferase 1, DNA polymerase l, ribonuclease A, lipoxygenase, matrix metalloproteinases, and lysozyme;
3. *Protein kinases*: protein kinase C, viral sarcoma, glycogen synthase kinase-3β, ErbB2 (HER2/neu), and phosphorylase kinase;

4. *Protein reductases*: thioredoxin reductase and aldose reductase;
5. *Carrier proteins*: casein, albumin, fibrinogen, *β*-lactoglobulin, and immunoglobulin;
6. *Other proteins*: cell survival proteins such as Bcl-2, cytoskeletal proteins such as FtsZ, and homotetrameric proteins such as transthyretin; and
7. *Tubulin*.

1.3.1.3.2 Chemical Modification Study on Curcumin

With an aim to improve the bioactivity as well as bioavailability while retain a similar safety profile to curcumin, numerous curcumin analogs have been obtained through total synthesis or semi-synthesis (Bairwa et al. 2014; Lin et al. 2006a, b). Based on the structural features of curcumin, the modifications can be grouped into two series. In series I (Fig. 1.1), modifications were focused on the phenyl moiety. Various groups were substituted on the phenyl ring, or the phenyl rings were replaced by various heterocycles. In series II (Fig. 1.1), various linkers were used to connect the two phenyl ring moieties. According to the different type of the linkers, the modifications could be further grouped as: substitutions on the 1,6-heptadiene moiety (**IIa**, **IIb**, **IIc**, Fig. 1.1), forming a heterocycle on the 1,6-heptadiene moiety (**IId**, Fig. 1.1), altering the conjugation of the 1,6-heptadiene moiety (**IIe**, Fig. 1.1), and changing the β-diketone to a monocarbonyl moiety (**IIf**, **IIg**, **IIh**, Fig. 1.1). The analogs produced were assayed for their antioxidant, anti-inflammatory, cytotoxic, anti-malarial, anti-HIV, antitrypanosomal, or antileishmanial effects. The results showed that the modifications can affect the bioactivity, and some new derivatives have exhibited improved activity as well as drug profile. However, no common structure–activity relationship (SAR) correlations could be concluded from these modifications.

1.3.1.3.3 Preclinical and Clinical Research on Curcumin and Its Derivatives in the Areas of Inflammation, Chemoprevention, and Cancer

Extensive research conducted on cell cultures, animal models, and clinical trials indicated that curcumin may have potential as a therapeutic agent in inflammatory bowel disease, pancreatitis, arthritis, and chronic anterior uveitis. Research shows that curcumin can interact with numerous molecular targets involved in inflammation. Curcumin modulates the inflammatory response by downregulating the activity of cyclooxygenase-2 (COX-2), lipoxygenase, and inducible nitric oxide synthase (iNOS) enzymes, inhibiting the production of the inflammatory cytokines tumor necrosis factor-alpha (TNF−α), interleukin (IL)-1, -2, -6, -8, and -12; monocyte chemoattractant protein (MCP); and migration inhibitory protein and downregulating mitogen-activated and Janus kinases.

Several clinical trials of curcumin were conducted for various inflammatory conditions, including postoperative inflammation, arthritis, uveitis, inflammatory

pseudotumors, dyspepsia, irritable bowel syndrome, inflammatory bowel disease, pancreatitis, and *Helicobacter pylori* infection. Most studies have been promising and warranted further research on curcumin's therapeutic value for treatment of inflammatory conditions (Jurenka 2009). For example, studies proved curcumin to be superior to phenylbutazone and placebo in reducing spermatic cord edema, which resulted from surgery for inguinal hernia or hydrocele (Satoskar et al. 1986). In a preliminary double-blind, randomized, controlled trial (RCT), curcumin given at 1,200 mg daily was effective in improving joint swelling, morning stiffness, and walking time (Deodhar et al. 1980). In a clinical trial involving 32 patients with anterior uveitis, after administrating 375 mg curcumin for 12 weeks, visual acuity and aqueous flare improvements and decrease in keratic precipitates were observed (Lal et al. 1999). Curcumin was also used for idiopathic orbital inflammatory pseudotumors (IOIP). In a small study of eight patients with IOIP, 375 mg curcumin three times daily was given for 6–22 months, until complete regression of symptomology was achieved. Patients were followed for 2 years and assessed at 3-month intervals. Only five patients completed the study, but four completely recovered on curcumin therapy (Lal et al. 2000). Moreover, in several clinical trials and a pilot study, curcumin demonstrated anti-inflammatory activity and therapeutic benefit in various gastrointestinal conditions, including dyspepsia, *Helicobacter pylori* infection, peptic ulcer, irritable bowel syndrome, Crohn's disease, and ulcerative colitis. Besides the examples mentioned above, numerous clinical trials are ongoing to explore the effect of curcumin on various inflammatory conditions. Jurenka has published an excellent review on this topic (Jurenka 2009).

It is well acknowledged that proinflammatory states are related to tumor promotion. Accordingly, the chemopreventive activity of curcumin has also been widely explored. Preclinical cancer research has shown that curcumin can inhibit carcinogenesis in various cancer types, such as colorectal, pancreatic, gastric, prostate, hepatic, breast, and oral cancers, as well as leukemia, and at various stages of carcinogenesis (Aggarwal et al. 2003). Several animal studies demonstrated that curcumin can inhibit all three stages of carcinogenesis: initiation, promotion, and progression. In the initiation and promotion stages, curcumin modulates transcription factors controlling phases I and II detoxification of carcinogens; downregulates proinflammatory cytokines, free-radical-activated transcription factors, and arachidonic acid metabolism via cyclooxygenase and lipoxygenase pathways; and scavenges free radicals. In the promotion and progression stages of carcinogenesis, curcumin decreases frequency and size of tumors and induces apoptosis via suppression of NF-kB and AP-1 in several cancer types (Chan 1995; Hong et al. 2004; Jurenka 2009; Kawamori et al. 1999; Singh and Aggarwal 1995). Currently, there are at least three ongoing clinical trials exploring the preventive benefits of curcumin as therapy to treat patients with adenomatous polyps at risk for colorectal cancer (Jurenka 2009).

In cancer therapy clinical trials, curcumin alone, as well as combinations with other agents such as bioperine and ashwagandha, was used to treat rectal cancer, pancreatic cancer, multiple myeloma cancer, osteosarcoma, or oral mucositis (Jurenka 2009). For example, one clinical trial indicated that curcumin can stabilize disease progression in patients with advanced pancreatic cancer. Twenty-one

patients received 8 g of curcumin daily until the disease progressed. One patient achieved disease stabilization for 18 months (Dhillon et al. 2008).

JC-9 (**7**, also known as ASC-J9, Table 1.1), a synthetic derivative of curcumin, exhibited potent activity against PC-3 (IC_{50} 1.1 μM) and LNCaP (IC_{50} 1.3 μM) cell lines (Lin et al. 2006a, b). Furthermore, JC-9 was found to be active in vivo against hepatocellular carcinoma and bladder cancer (Ma et al. 2008; Miyamoto et al. 2007). The mechanism of action study indicated that JC-9 enhances androgen receptor degradation (Shi et al. 2009). Another study indicated that JC-9 and its derivatives can overcome EGFR-TKI lung adenocarcinoma drug resistance and reduce EGFR-TKI-induced GI adverse effects (Wada et al. 2015). Therefore, JC-9 is a potential clinical trial candidate for treating prostate cancer, liver cancer, bladder cancer, and other cancers. JC-9 was licensed by AndroScience Corp. (San Diego, CA) and succeeded in phase 2 clinical trials against acne in 2014. Moreover, antiprostate clinical trials with JC-9 are being planned (Itokawa et al. 2008; Lee et al. 2008).

1.3.1.4 Conclusion

Turmeric has been used in traditional medicine since ancient times with a wide spectrum of therapeutic areas. Enormous amounts of data from preclinical and clinical research have confirmed turmeric's benefits as described in traditional medicine. However, clinical applications of turmeric as a botanical drug can be made only after extensive research on its bioactivity, mechanism of action, pharmacotherapeutics, and toxicity, as well as developing standard QC. Curcumin is the major biologically active constituent of turmeric. In spite of numerous reports showing its putative mechanism(s), multiple molecular targets, and wide range of therapeutic applications, curcumin has not yet been approved for treatment of any human disease, even though it has been reported to be safe for humans at gram dosages. The main obstacle to utilizing curcumin therapeutically is its poor systemic bioavailability. Also, because curcumin can bind to multiple signaling molecules, it is rather difficult to determine which target is causing the desired effect in a certain disease. Therefore, further study should be focused on designing additional different curcumin analogs that will be more effective and better absorbed, as well as on developing a clearer understanding of the actual functional meaning of direct interactions of curcumin with various specific targets. Such discoveries will help to elevate this fascinating natural product as a therapeutic agent for the treatment of human diseases.

1.3.2 Antrodia camphorata

1.3.2.1 Introduction

Antrodia camphorata (syn. *Antrodia cinnamomea*, *Taiwanofungus camphoratus*) is a unique basidiomycete fungus of the Fomitopsidaceae family. It is a parasite that affects the inner cavity of *Cinnamomum kanehirae* Hayata (Lauraceae) (bull

camphor tree), which grows only in Taiwan with a distribution in broad-leaved forests at an altitude of 200–2,000 m (Chang and Chou 1995). *A. camphorata*, also called "Niu-chang-chih" (牛樟芝), "Chang-chih," "Niu-chang-ku," or "Chang-ku" in Taiwan, is used to lessen the discomforts caused by alcohol drinking or exhaustion and is believed to be beneficial to preserve human vitality and promote longevity. Moreover, it has been used in TCM to treat a number of illnesses including diarrhea, abdominal pain, hypertension, itchy skin, viral infection, stomatitis, diabetes mellitus, nephritis, proteinuria, liver cirrhosis, hepatoma, influenza, car sickness, heat-related fever, and motion sickness (Geethangili and Tzeng 2011; Wu and Ryvarden 1997). Therefore, in Taiwan, *A. camphorata* is also called as "ruby in mushroom."

Production of *A. camphorata* can occur by gathering mature fruiting bodies of wild *A. camphorata*, wood or solid-state cultivation, and liquid-state fermentation. Mature fruiting bodies of the wild *A. camphorata* are now close to extinction due to their very slow growth rate (1 or more years) and overharvesting (Huang et al. 2012).

1.3.2.2 Chemical Constituents

Currently, around 200 compounds have been identified from *A. camphorata*. These compounds have been summarized in four reviews (Ao et al. 2009; Geethangili and Tzeng 2011; Huang et al. 2012; Lu et al. 2013). Generally, the compounds isolated from *A. camphorata* include triterpenoids, diterpenoids, monoterpenes, steroids, lignans, benzoquinones, benzenoids, maleic/succinic acid derivatives, fatty acids and their esters, polysaccharides, etc. Terpenoids are the main chemical constituents of fruiting bodies of *A. camphorata*. Among the over 40 isolated terpenoids, most of them are lanostane (**III**, Fig. 1.2) and ergostane (**IV**, Fig. 1.2) triterpenes.

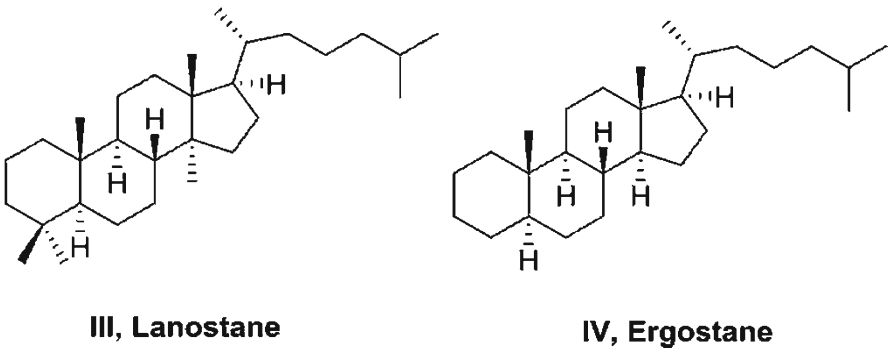


Fig. 1.2 Most common triterpene skeletons found in *Antrodia camphorata*

1.3.2.3 Pharmacological Effects

Various crude extracts of *A. camphorata*, such as ethanol/methanol, chloroform, ethyl acetate, and aqueous extracts, have been tested for their pharmacological effects in vivo and in vitro in different modes. These research efforts indicated that *A. camphorata* possesses versatile bioactivities, including anticancer activity, anti-inflammatory and immunomodulatory effects, inhibition of hepatitis B virus (HBV) replication, antioxidant properties, antimicrobial activity, hepatoprotective effects, prevention of liver fibrosis, neuroprotective activity, antihypertensive effects, vaso-relaxation properties, antihyperlipidemic activity, and cardiovascular effects (Ao et al. 2009; Geethangili and Tzeng 2011; Huang et al. 2012; Lu et al. 2013).

Beside the crude extract, various pure natural products from *A. camphorata* have also been widely studied and found to exhibit cytotoxic, neuroprotective, anti-inflammatory, anti-insecticidal, anti-HBV, and anti-HCV effects. For example, several triterpenoids, such as camphoratins B–F and zhankuic acid A, showed moderate to potent cytotoxicity, with EC_{50} values ranging from 0.3 to 3 μM against KB and KB-VIN human cancer cell lines. Moreover, camphoratins F and J, as well as zhankuic acid A and their related compounds, were also found to exhibit anti-inflammatory NO production inhibition activity with IC_{50} values of less than 5 μM and were more potent than the nonspecific NOS inhibitor nitro-L-arginine methyl ester (Shi et al. 2011; Wu et al. 2010).

Antroquinonol (**8**, Table 1.1), antroquinonol B, antroquinonol C, and related compounds are ubiquinone derivatives isolated from mycelia, fruiting bodies, or both of *A. camphorata*. Antroquinonol was reported to exhibit cytotoxic activities against cancer cell lines MCF-7, MDA-MB-231, Hep 3B, Hep G2, DU145, and LNCaP with IC_{50} values ranging from 0.13 to 6.09 μM (Lee et al. 2007). Golden Biotechnology Corp. of Taiwan patented the application of antroquinonol and its related compounds for inhibiting the growth of breast, lung, hepatic, and prostate cancers (Liu et al. 2008). Antroquinonol (Hocena®) has completed a phase 1 study in the USA (https://clinicaltrials.gov/ct2/show/NCT01134016), and a phase 2 study is planned to treat non-small cell lung cancer (https://clinicaltrials.gov/ct2/show/NCT02047344). It was granted Orphan Drug Designation by the US FDA for pancreatic cancer (January 21, 2015), acute myeloid leukemia (April 30, 2015), and hepatocellular cancer (July 23, 2015).

1.3.2.4 Conclusion

The pharmacological effects of an extract or isolates from *A. camphorata* have been widely studied for decades. However, most studies have been performed in vitro and in vivo with animals. Next, more clinical studies are expected to confirm the therapeutic benefit of *A. camphorata*. Although over 200 compounds have been isolated, little research regarding modification and synthesis of active compounds has been conducted. Therefore, continued medicinal chemistry study on *A. camphorata* may help to provide more promising leads for drug development. Also, it is urgent to

establish standard quality control and methods for developing the crude extract of *A. camphorata* as a botanical drug that could be accepted worldwide.

1.3.3 Apium graveolens

1.3.3.1 Introduction

Apium graveolens Linn. (celery, Han Qin, 旱芹, Umbelliferae), belonging to the family Apiaceae, is a common annual herb widely cultivated in temperate zones. Its leaf stalks are consumed as a popular vegetable. In various forms, such as fresh herb, stalk, leaves, seeds, seed oil, and oleoresin, celery is used to flavor foods. Celery stalks have shown a broad bioactivity spectrum, including antihyperlipidemic, antihypertensive, and memory enhancement effects (Anonymous 2009). Its seeds are used for treatment of bronchitis, asthma, and diseases of the liver and spleen (Satyavati and Raina 1976).

1.3.3.2 Chemical Constituents

The chemical constituents of the whole herb are represented by psoralen, bergapten, isopimpinellin, luteolin, apiin, chrysoeriol, apigenin, quercetin, and volatile oils including d-limonene, myrcene, isobutyric acid, valeric acid, 3-isobutylidenephthalide, 3-isovalidenephthalide, and cis-3-hexen-1-yl-pyruvate. Celery seeds contain various bioactive compounds, including phthalides, coumarins, flavonoids, sesquiterpenoids, and aromatic glucosides. The seed oil is a valuable product in both the flavor and fragrance industries. 3-*n*-Butylphthalide, 3-*n*-butyl-4,5-dihydrophthalide (sedanenolide), and sedanolide are reported to be the major flavor components of the seed oil. The volatile oils of the leaves were reported to contain octene-4,5-dione, 2-isopropyloxyethane, sabinyl acetate, 1,4-butanediol, seselin, rutaretin, celereoin, celeroside, apiumoside, isoquercitrin, vellein, apiumetin, nodakenin, myristic acid, 8-hydroxy-5-methoxypsoralen, umbelliferone, and nodakenetin (Anonymous 1999a).

1.3.3.3 Bioactivity

Celery has been used as a medicinal plant for its aphrodisiac, anthelmintic, antispasmodic, carminative, diuretic, laxative, sedative, stimulant, and tonic effects. The medicinal parts of the plant are the roots, leaves, and seeds. Products of celery are also used for blood purification, for regulating bowel movements for evacuation, for glandular stimulation, and as a cure for gallstones and kidney stones. Celery seeds are implicated in arthritic pain relief and for treating rheumatic conditions and gout. Celery is also effective at lowering blood pressure due to the 3-*n*-butyl phthalide

constituent, which has been demonstrated to relax the smooth muscles that line blood vessels (Anonymous 1999a).

Various extracts or fractions of celery were reported to possess antioxidant activity, anti-inflammatory effect, hepatoprotective activity, antimicrobial activity, and inhibition of blood platelet aggregation. Coumarins isolated from celery were reported to help prevent free radicals from damaging cells, thus decreasing the mutations that increase the potential for cells to become cancerous (Sowbhagya 2014).

S-(-)-3-*n*-butylphthalide [*S*-(-)-3-butyl-1(3*H*)-isobenzofuranone, *S*-(-)-NBP, **9**, Table 1.1] was isolated from celery seeds. Pharmacological studies indicated that s-(-)-NBP, as well as synthesized (±)-NBP, has anti-ischemic effects. When stroke-prone spontaneously hypertensive rats were pretreated with (±)-NBP, the onset of stroke was delayed, life span was prolonged, and the neurological deficit score was decreased. (±)-NBP was also reported to ameliorate brain edema and blood–brain barrier damage in middle cerebral artery-occluded rats. (±)-NBP may have neuroprotective effects, since it improved mitochondria dysfunction. S-(-)-NBP and (±)-NBP also exhibited an inhibitory effect on thrombus formation in rats (Zhu et al. 2004). (±)-NBP has been developed as an anti-cerebral ischemic drug and has completed or is ongoing in phase 2–4 clinical trials in China (https://clinicaltrials.gov/ct2/show/NCT02149875, NCT01405248, NCT00724724, and NCT02594995). The results from the completed clinical trials confirmed its effect for treatment of mild and moderate acute ischemic stroke. In phase 2 trials, the total rate of efficacy was 70.3 % among the 91 effective cases. Phase 3 trials indicated that, in 282 effective cases, the total rate of efficacy was 63.9 %. In phase 4 trials, among the two groups with 305 and 1,147 effective cases, the efficacy ratios in the two groups were 78.4 % and 78.2 %, respectively. (±)-NBP was approved by the State Food and Drug Administration (SFDA) of China in 2005 for the treatment of ischemic stroke.

1.3.3.4 Conclusion

Celery and the natural products isolated from celery have exhibited great health benefits. The approval of (±)-NBP by the China SFDA for treating ischemic stroke is an excellent accomplishment. Nevertheless, further study on (±)-NBP-related compounds is still needed for meeting the approval from the US FDA, so that the world-class anti-stroke drugs can be obtained.

1.3.4 Momordica charantia

1.3.4.1 Introduction

In TCM, plants with a bitter flavor and cold property have long been used in the treatment of diabetes and high blood sugar (Chen et al. 2015). *Momordica charantia* (Chinese: ku gua 苦瓜), known as bitter melon or bitter cucumber, is a common

edible vegetable, although all parts of the plant have also been used medicinally. The plant is a tropical and subtropical vine belonging to the family Cucurbitaceae, which produces a warty or ridged oblong fruit. Although it is bitter, the rind of the green fruit is often eaten cooked in stir fries in Chinese cooking or curries in Southeastern dishes. When the fruit is fully ripe, the rind is extremely bitter, but the red pith is sweet. In Japanese Kampo medicine, bitter melon is used for the depletion of yin and, thus, to treat yin stages of chronic diseases such as diabetes (Rister 1999). Indeed, the antidiabetic potential of this plant species has gained significant scientific attention (Broadhurst et al. 2000; Chaturvedi 2012; Grover and Yadav 2004; Horax et al. 2010; Hsu et al. 2011; Wang et al. 2012), particularly regarding the hyperglycemic effects of various chemical components.

1.3.4.2 Chemical Constituents

Components of this plant include flavonoids, isoflavones, anthroquinones, glucosinolates, steroidal saponins, glycol alkaloids, cucurbitane triterpenoids (e.g., charantin (**10**, Table 1.1)), and polypeptides (e.g., polypeptide-p) (Hamid et al. 2015; Hung et al. 2012; Kaur et al. 2016; Medagama and Bandara 2014; Snee et al. 2011; Tan et al. 2008). As many of these compounds have a bitter taste (Drewnowski and Gomez-Carneros 2000), studies have been conducted to determine how to best mask the bitter taste, if wider acceptance and consumption of *M. charantia* is to be promoted for medicinal value (Snee et al. 2011). The phytochemistry of the plant, particularly regarding antidiabetic constituents, has been well reviewed (Grover and Yadav 2004; Joseph and Jini 2013; Raman and Lau 1996).

1.3.4.3 Bioactivity

Bitter melon has been used as a folk medicine for numerous conditions, including stomach and gastrointestinal disorders (e.g., to treat colic in infants and peptic ulcers in adults as well for carminative, laxative, or purgative effects) (Grover and Yadav 2004). However, in traditional uses and modern medical studies (Joseph and Jini 2013; Raman and Lau 1996), the plant has been mostly appreciated for its ability to relieve diabetes by improving glucose metabolism (Hasan and Khatoon 2012; Leung et al. 2009), although it has also been studied for anticancer, antiviral (including HIV, herpes, polio), analgesic, anti-inflammatory, and hypotensive effects (Grover and Yadav 2004; Snee et al. 2011).

Among the compounds listed above, cucurbitane-type triterpenoids have been linked to AMP-activated protein kinase activity as a possible hypoglycemia mechanism (Tan et al. 2008), while polypeptide-p mimics the action of human insulin and might be used as a plant-based insulin replacement (Paul and Raychaudhuri 2010).

An exciting recent development is the discovery of a potential novel antidiabetic protein. *Momordica charantia* insulin receptor (IR)-binding protein (*mc*IRBP) is a novel insulin receptor (IR)-binding polypeptide with a distinct binding site from

that of insulin (Lin et al. 2014). However, *mc*IRBP also enhances glucose uptake in cells and clearance in normal and diabetic mice, likely via stimulation of similar biopathways as insulin and regulation of genes affecting glucose and lipid metabolism (Lin et al. 2014).

1.3.4.4 Conclusion

Momordica charantia offers an alternative treatment to both injectable insulins, the only treatment for type 1 diabetes and current oral type 2 antidiabetic drugs, including sulfonylureas/insulinotropics, biguanides, α-glucosidase inhibitors, thiazolidinediones, and gliptins. Further studies and strictly controlled clinical trials are needed to evaluate thoroughly the potential of *mc*IRBP to treat diabetes, a life-altering metabolic disease, which can lead to blindness, renal disease, lower extremity amputations, and even death.

1.3.5 Monascus purpureus

1.3.5.1 Introduction

Red mold rice (RMR) is produced from ordinary rice by fermentation with the yeast species *Monascus purpureus* (Chinese: 紅麴). In East Asia, RMR is used to flavor, color, and preserve food and medicinally to improve blood circulation and digestion, as well as to treat diabetes (Heber et al. 1999; Li 1596).

1.3.5.2 Chemical Constituents

The fermentation process produces various secondary polyketide metabolites (Li 1596; Ma et al. 2000), including monascin (**11**, Table 1.1), ankaflavin (**12**, Table 1.1), and several monacolins.

1.3.5.3 Bioactivity

The hypolipidemic and hypocholesterolemic effects of these compounds have been noted for many years (Endo 1979; Lee et al. 2010). Indeed monacolin K (**13**, Table 1.1) is the same compound now widely marketed as the cholesterol-lowering drug lovastatin. RMR has also been studied for its anti-obesity effects, which have been linked to its lipolytic activity and subsequent prevention of body fat accumulation (hypertrophy and hyperplasia of adipose tissue), as well as mild appetite suppression (Chen et al. 2008). Finally, RMR fermented with *M. purpureus* strain NTU 568 [found to produce a higher content of the active components (Shi and Pan

2011)] has been developed as a commercial functional food to prevent Alzheimer's disease (AD) (Lee and Pan 2011a, b).

1.3.5.4 Conclusion

These fermented products hold promise for preventive medicine, particularly decreasing heart disease risk. Continued studies are aimed at identification of the neuroprotective metabolites in RMR, further evaluation of their mechanism of action, and structural modifications to improve pharmacological profiles as potential drugs for neurodegenerative disorders, including AD and Parkinson's disease (Lin et al. 2015).

1.3.6 Astragalus membranaceus

1.3.6.1 Introduction

The roots of *Astragalus membranaceus* (Chinese: Huang Chi 黃耆) (known in TCM for sweet flavor, slightly warm property) are used in various TCM formulas to counteract symptoms associated with a deficiency of chi, e.g., low energy, lack of strength, anorexia, slow healing, etc. (Batch 2010). As the authors have previously provided a detailed description of this herb (Lee et al. 2013), this section will focus only on the studies of PG2, an IV injection used to alleviate cancer-related fatigue and improve the quality of life for cancer patients.

1.3.6.2 Chemical Constituents

Polysaccharide immunostimulatory principles were developed as PG2 by Pharmagenesis in the USA and PhytoHealth Corporation of Taiwan based on the initial advice of Dr. K.H. Lee (Lee et al. 1993).

1.3.6.3 Bioactivity

In a randomized, double-blind placebo-controlled phase 2/3 clinical study (https://clinicaltrials.gov/ct2/show/NCT00523107), patients with advanced cancer who experienced moderate to severe cancer-related fatigue (CRF) had a higher response rate when they received PG2 compared with patients who received a placebo (normal saline). This study concluded that PG2 could be effective and safe for managing CRF in advanced cancer patients, without major or irreversible toxicities (Chen et al. 2012). Subsequently, PG2 was approved for clinical use in treating CRF by the Taiwan Department of Health in April 2011, particularly in cancer patients who

developed severe fatigue after receiving chemotherapy. In another clinical trial, a combination treatment with PG2 and platinum-based chemotherapy in non-small cell lung cancer patients led to improved quality of life indices, including management of fatigue, nausea, vomiting, pain, and appetite loss (Kuo et al. 2015). Recruitment is currently ongoing for a phase 4 clinical trial (https://clinicaltrials.gov/ct2/show/NCT01720550) to evaluate the use of different doses of PG2 treatment for fatigue improvement in advanced cancer patients who are under standard palliative care in a hospice setting. Currently, all clinical studies have been performed with an IV injectable form of PG2.

1.3.6.4 Conclusion

In addition to the clinical studies, gene expression profiling showed that PG2 product batches were of high quality and consistency as well as functionally equivalent regarding their effects on the immune and hematopoietic systems (Kuo et al. 2015). A bioinformatics-based approach provided a quantitative measurement for the quality and consistency of herbal medicines and revealed new roles (e.g., immune modulation) for PG2 in cancer treatment. In the same study, PG2 and doxorubicin acted synergistically on induced cell death in HL-60 cells, raising the possibility of a novel antitumor function for PG2. Also, clinical trials (http://www.phytohealth.com.tw/upimages/newarrival1121228011612.pdf) are being performed with PG2 in Taiwan for potential use in treating stroke, both hemorrhagic and ischemic.

1.3.7 Huang Chin Tang

1.3.7.1 Introduction

Huang Chin Tang (or *Scutellaria* decoction) has been used as a Chinese herbal medicine for over 1,800 years to treat various GI issues, including diarrhea, nausea, vomiting, and abdominal cramps, as well as fever and headaches.

1.3.7.2 Chemical Constituents

Huang Chin Tang contains the four herbs shown below in a 3:2:2:2 ratio.

- *Scutellaria baicalensis* (Chinese: Huang Qin 黄芩) (common: skullcap): part used – root, main purpose – to regulate digestive and intestinal functions
- *Paeonia lactiflora* (Chinese: Bai Shao 芍藥) (common: white peony): part used – root, main purpose – combines with *Glycyrrhiza* to relax abdominal cramps
- *Glycyrrhiza uralensis* (Chinese: Zhi Gan Cao 炙甘草) (common: licorice): part used – root, main purpose – combines with *Paeonia* to relax abdominal pain and

cramps as well as to harmonize all ingredients and diminish side effects due to the more harsh components, such as *Scutellaria*

- *Ziziphus jujuba* (Chinese: Da Zao 大棗) (common: jujube, Chinese date): part used – fruit, main purpose – to stimulate digestive functions

Thus, this Chinese medicine formulation is a complex mixture containing numerous compounds, unlike Western drugs, which usually contain only a single compound. Liquid chromatography and tandem mass spectrometry have been used to identify various chemicals, including flavonoids, triterpene saponins, and monoterpene glycosides, as well as assign them to the four individual herbs from PHY906, a carefully prepared, consistent, quality-controlled formulation of Huang Chin Tang for cancer therapy (Ye et al. 2007). Flavonoids, such as baicalein (**14**, Table 1.1), are major active compounds from *Scutellaria*.

1.3.7.3 Bioactivity

While cancer chemotherapeutic drugs can lengthen the life of a cancer patient, their toxicities and side effects can also severely diminish the quality of that life. PHY906 showed promising results in phase 1 clinical trials in 2010 (Saif et al. 2010) and provided relief from chemotherapy-induced gastrointestinal toxicity, especially severe diarrhea. While PHY906 did not affect the initial intestinal DNA damage caused by irinotecan, it did encourage regeneration of the intestinal progenitor or stem cells and several signaling components, ultimately restoring the intestinal epithelium. Other simultaneous action modes were also evident (Lam et al. 2010). Notably, in addition to reducing irinotecan-induced toxicities, PHY906 could potentiate the drug's anticancer activity and exert favorable actions in multiple cancers treated with numerous chemotherapy drugs acting by different mechanisms (Liu and Cheng 2012). In a 2014 phase 2 clinical trial, a combination of PHY906 and capecitabine, a prodrug of 5-FU, was found to be a viable option for patients with advanced pancreatic cancer treated previously with gemcitabine (Saif et al. 2014). In the small cohort, quality-of-life indices of hand-to-foot syndrome and diarrhea were improved, and median overall survival was extended, especially in two patients with partial responses (69 and 83 weeks) compared with the previously reported 2 months for other second-line salvage therapies (Kang and Saif 2008). In a recently reported study, PHY906 potentiated the anti-hepatoma activity of the drug sorafenib by multiple mechanisms, particularly attraction of macrophages with a higher M1/M2 (tumor rejection) expression (Lam et al. 2015).

1.3.7.4 Conclusion

Based on the studies above, this CHM formula shows great promise as an adjuvant cancer therapy.

1.3.8 Eucommia ulmoides

1.3.8.1 Introduction

Eucommia ulmoides (Chinese: Tu Chung 杜仲) is a unique tree called the hardy or hard rubber tree and originating in central China. The most medically useful plant parts are the stem bark and leaves, used to make Tu Chung tea. This tea is considered to be useful in blood pressure regulation and weight control, as well as to rejuvenate skin elasticity and strengthen the lower back and knees. *Eucommia* is, thus, known as a "longevity herb" with its continued use thought to slow the aging process by improving body metabolism and strengthening the muscular skeletal system. *Eucommia* is well known in the traditional medicines of China, Japan, and Korea and is mentioned in the Chinese classic *Shennong Bencaojing* Yang (1998). It has analgesic (especially for pain in the lower back and knees), tonic (particularly for right kidney yang), and hypotensive actions. Regarding the former action, *Eucommia* is likely best known as part of the TCM arthralgia remedy *Duhuo Jisheng Tang* and is used to treat rheumatoid arthritis, rheumatic back pain, and sciatica (Dharmananda 1999, 2000). In most traditional formulations, *Eucommia* is a relatively minor ingredient in a large combination of herbs, e.g., it is 7% of *Duhuo Jisheng Tang*; however, together with *Dipsacus asperoides*, it is a major component of *Duzhong Wan*, a TCM for treating lower back pain during pregnancy (Huang et al. 2014).

1.3.8.2 Chemical Constituents

Numerous chemical constituents and pharmacological activities of *Eucommia ulmoides* have been described (Deyama et al. 2001; Lee et al. 2012). The main chemical components of interest about the traditional use of Tu Chung are iridoid glycosides, including geniposidic acid and aucubin, and lignans, such as pinoresinol glucoside and diglucoside.

1.3.8.3 Bioactivity

Various lignans have been linked to antihypertensive and vasodilating effects (Deyama et al. 2001; Luo et al. 2010; Sih et al. 1976). In mechanistic studies (Jin et al. 2008), the vasodilation induced by an aqueous extract of *Eucommia ulmoides* was found to depend on endothelium-derived hyperpolarizing factor (EDHF) with the activation of K^+ channels. In addition, muscarinic Ach receptor agonists could also play a role in lowering blood pressure via vasodilation. Geniposidic acid (**15**, Table 1.1) also has antihypertensive effects (Deyama et al. 2001), while aucubin (**16**, Table 1.1) and other iridoids are likely responsible for the anti-inflammatory effects of *Eucommia*. Aucubin inhibits the arachidonic acid pathway,

TNF-α-induced responses, and NF-kB activation (Benito et al. 2000; Park 2013), which may partly explain the herbal use in the treatment of arthritis (Wang et al. 2015b), as well as indicate a potential for improving obesity-induced atherosclerosis (Park 2013). Aucubin and geniposidic acid promoted collagen synthesis (Li et al. 1998), and geniposidic acid increased the skin moisture content of UV-damaged skin in hairless mice (Jimbo et al. 2015). Due to the important pharmacological effects of geniposidic acid and aucubin, a high-performance liquid chromatography – tandem mass spectrometry method has been developed to determine these two compounds in rat plasma, particularly for the pharmacokinetic study after oral administration of *Eucommia* herbal tea (Zhang et al. 2014). Due to its medicinal values, geniposidic acid is used as a food additive in Japan (Zhang et al. 2014).

Neuroprotective properties have also been ascribed to *Eucommia ulmoides* aqueous bark extracts, implying potential application in the prevention or treatment of Alzheimer's and other neurodegenerative diseases (Kwon et al. 2012, 2014). *Eucommia* leaves have also been made into a health beverage (Yue et al. 1999).

1.3.8.4 Conclusion

Eucommia ulmoides is a TCM recommended for vitality enhancement and longevity. In addition to fairly common plant flavonoids, it also contains less common lignans and iridoid compounds. More scientific studies are needed to verify the plant's suggested role as a "longevity herb" in preventing bone loss, inducing fat loss, and reducing elevated blood pressure and triglycerides. However, its potential as a nutritional supplement is fairly high, because, unlike many other plants, it is active at relatively low oral dosages.

1.3.9 Ligusticum wallichii *(or* Cnidium officinale*)*

1.3.9.1 Introduction

In TCM, the rhizomes from *Ligusticum wallichii* or *L. chuanxiong* (Chinese: Chuan Chung or Chuan Xiong 川芎), plant species in the carrot family (Umbelliferae), are well known for both medicinal (to treat/prevent disease) and edible (to provide nutrition) uses. In Japanese Kampo medicine, the roots of *Cnidium officinale* are used for the same purposes. Commonly, the plant is known as a lovage root and is particularly used as an important herb in blood tonics, for treating pain from headache, rheumatic arthralgia, or traumatic injury and to relieve gynecological problems. Si Wu Tang (four-substance decoction) is one of the most famous gynecological TCM formulas containing *Ligusticum*, as well as *Angelica sinensis* (Dang Gui), *Rehmannia* (Sheng Di Huang), and *Paeonia alba* (Bai Shao) (Zhou and Qu 2009). This formula is used for treating menstrual disorders, such as amenorrhea and dysmenorrhea.

1.3.9.2 Chemical Constituents

Ligusticum roots contain other important bioactive compounds, including alkaloids, particularly tetramethylpyrazine; phthalides, such as ligustilide and senkyunone; organic acids, such as ferulic acid; anthraquinones, such as chrysophanic acid; polysaccharides; ceramides; and cerebrosides (Li et al. 2012b).

1.3.9.3 Bioactivity

Pharmacological studies have shown that *Ligusticum* TCM formulas and particularly its antihypertensive constituent tetramethylpyrazine (**17**, Table 1.1), also known as ligustrazine or chuanxiongzine, can increase coronary circulation and decrease oxygen consumption, increase myocardial contractility and decrease heart rate, and cause vasodilation and lower blood pressure (Lee 2015). A review (Ran et al. 2011) compiled the current scientific research on the chemistry and pharmacology of *L. chuanxiong*, pointing out its valuable therapeutic properties as well as medical potential. The pharmacological targets and pharmacokinetics of *L. chuanxiong*, as well as other TCM formulas used for the treatment of cardiovascular and cerebrovascular disease, have been studied with the aims of clarifying the traditional uses and modernizing these herbal medicines (Li et al. 2012a; Zeng et al. 2013).

1.3.9.4 Conclusion

As *Ligusticum* is widely used in TCM for treating migraine, the herb's effects on the blood–brain barrier have been studied (Wang et al. 2015a). The alkaloid tetramethylpyrazine has also shown in vivo nootropic and neuroprotective effects in rat models (Kong et al. 2015; Lu et al. 2014; Wu et al. 2013), as well as in vitro actions against neuro-inflammation (Kim et al. 2014), giving it a possible use in treatment of Alzheimer's or other neurodegenerative diseases, which could greatly improve quality of life for many elderly adults.

1.3.10 Lycium barbarum

1.3.10.1 Introduction

Lycium barbarum (Chinese: Kou Chi Tzu 枸杞子) is a species of boxthorn in the family Solanaceae. It produces a bright red-orange oblong fruit, known as a wolfberry or goji berry. In China, these sweet-tasting berries are celebrated in an annual festival each August in Ningxia province, China, the main location of their cultivation. The berries can be eaten either raw or dried; made into juice, wine, or tea; or

processed into powders, tablets, and tinctures (Cheng et al. 2015). In TCM, the berries (*Fructus lycii*) are regarded to benefit the liver and kidney, replenish vital essence (chi), and improve eyesight. The root bark (*Cortex lycii*) is also used to alleviate fever and to treat night sweats, pneumonia, and cough (Potterat 2010; Yao et al. 2011).

1.3.10.2 Chemical Constituents

L. barbarum fruits are rich in polysaccharides/proteoglycans (5–8 % of the dried fruit), termed LBPs, from six carbohydrates: galactose, glucose, rhamnose, arabinose, mannose, and xylose. Other major compounds are the coumarin scopoletin and glycosylated vitamin C (2-*O*-β-D-glucopyranosyl-L-ascorbic acid) (Tang et al. 2012). Water-soluble LBPs can be separated by an extraction process to remove more lipid-soluble constituents, including carotenoids such as zeaxanthin (Cheng et al. 2015). The LBPs are considered to be the most important, bioactive components (Shan et al. 2011). Other components in the fruit are carbohydrates, carotenoids, flavonoids, betaine, cerebroside, β-sitosterol, amino acids, trace elements, vitamins, etc. (Amagase and Farnsworth 2011). Detailed phytochemical reviews are available (Potterat 2010; Yao et al. 2011).

1.3.10.3 Bioactivity

In TCM, plants from the genus *Lycium*, including *L. barbarum* and the related species *L. chinense*, have been used for tonic, aphrodisiac, hepatoprotective, antiseptic, hypotensive, and hypoglycemic properties (Anonymous 1999c; Potterat 2010; Yao et al. 2011). The traditional "yin"-nourishing effect can be associated with immunoregulating actions. The LBPs exert both indirect effects on immune modulation and direct effects on cytoprotection, antiaging, and neuromodulation (Chang and So 2008). Such scientific evidence provides some support for the folk medicine use of wolfberries to increase longevity (Potterat 2010; Yao et al. 2011). Also, a recent report found that wolfberries can enhance the protective effect of influenza vaccine in older mice (Du et al. 2014). Similar support has also been found for the eye health benefits, e.g., LBPs have shown neuroprotective effects on retinal ganglion cells (Mi et al. 2013). LBPs have also been linked to immune-enhancing effects by increasing expression of interleukin-2 and tumor necrosis factor-alpha (Gan et al. 2003), as well as anticancer effects, such as apoptotic induction, stimulating interest in *Lycium* as a cancer therapy agent/adjuvant (Tang et al. 2012). The scientific studies related to the above bioactivities, as well as metabolism stimulation, cardiovascular benefits, diabetes, and antioxidant effects, have been well described in several reviews (Amagase and Farnsworth 2011; Cheng et al. 2015; Jin et al. 2013).

1.3.10.4 Conclusion

L. barbarum undoubtedly has nutritional value for public health, and its chemical components have shown various biological effects in cellular and animal studies, as well as some human clinical studies. Indeed, the Natural Standard Research Collaboration recently reported an evidence-based review to compile folkloric precedent with consolidated safety and efficacy data from the scientific literature (Ulbricht et al. 2015). However, further studies should be performed to truly clarify detailed mechanisms, possible synergistic effects, and ensured safety profiles, such as contraindication with other food and medications. The general public needs to be told about not only the potential health benefits but also the difference between health claims and structure–function claims regarding the potential of *Lycium*, as well as other products, as a functional food (Lasekan 2014).

1.4 Summary

Chinese herbal medicine (CHM) has been used for many thousands of years to both treat and prevent human disease. This invaluable knowledge makes CHM the best resource for modern scientists in their efforts to develop new drug research and future clinical trial candidates. Chronic disease seriously affects the quality of life of patients, and many ancient CHM-derived remedies could hold the answer to alleviating many of those diseases' most debilitating symptoms, as well as preventing those diseases at the outset and treating the disease once contracted. 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. 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 mixture of current Western medicine and the ancient therapies of CHM could indeed hold promising answers for the treatment of chronic diseases to greatly improve quality of life of patients, making CHM of the upmost importance in future drug discovery and development. As evidenced by the ten case studies outlined above, the active principles of CHM have been elucidated. Accordingly, there is a major need to develop these compounds into world-class medicines with great efficacy and low toxicity, making them superior to the current Western medicine therapies currently available.

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