ACTIVE PHYTOCHEMICALS FROM CHINESE HERBAL MEDICINES

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ANTI-CANCER ACTIVITES AND MECHANISMS

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CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Version Date: 20150622

International Standard Book Number-13: 978-1-4822-1987-6 (eBook - PDF)

I dedicate this book to my family: *my wife, Teresa, my two children, Yuen and Hang, and the memories of my mother, Tong Sam Mui, and of my father, Ho Tak Kam, who helped me with my career and bringing up my children.*

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Preface

This is the first book on integrated pharmacology of herbal medicines with a unique approach toward the development of phytochemicals and their mechanisms of actions in the context of cancers and the diseases they are used to treat. The book covers biologic actions of the active phytochemicals at the molecular, cellular, and organ levels. The first few chapters deal with the principles of the interaction of phytochemicals and the related drug actions. The book also covers the basic concepts of identification of active phytochemicals and their pharmacological actions. It provides insightful information on how our knowledge can be influenced by the biologic and chemical factors of phytochemicals. Conventional icons are used to explain the main molecular and cellular actions of phytochemicals for better understanding. These icons deal with the treatment of cancer and diseases treated with herbal phytochemicals in rats. Each body system addresses the common pathways affecting cancer development before discussing the phytochemical classes and specific phytochemicals that have been recently reported in journal papers for the management of cancer and other diseases. The readers are introduced to the increasingly important aspects of pharmacology, including health benefits and drawbacks of phytochemicals. In addition, relevant background of the biochemistry of cancer is provided. Necessary illustrations that depict relevant pharmacology that would enhance the understanding of phytochemical actions are included. Tables presenting their adverse actions are used to highlight important issues related to phytochemical actions. Prescription drugs are used to compare phytochemical actions in in vivo studies. Insights into how phytochemicals can be developed from herbal medicines with multiarrays of pharmacological activities are offered. We hope that this book will provide useful information and reference on phytochemicals obtained from herbal medicines and will contribute toward cancer drug development with herbal phytochemicals. It has been designed for medicinal scientists but will also be useful to pharmaceutical professionals and students interested in alternative medicines, as it bridges the gap between fundamental mechanisms of anticancer actions and the use of phytochemicals to manage cancers and other human diseases. We hope that the readers enjoy reading this book.

Author

Dr. Wing Shing Ho, PhD, is associate professor of the biochemistry programme at the School of Life Sciences in The Chinese University of Hong Kong, Hong Kong, China. He earned his BS in biochemistry (1979) from the University of Alberta and MA in chemistry (1982) and PhD in biological chemistry (1985) from the State University of New York at Buffalo. After completing a postdoctoral training in the pediatrics department at SUNYAB, he moved to the Department of Chemistry at the University of Utah as a postdoc investigating the methodology of isolation and purification of DNA and subsequently moved to the Center for Human Toxicology, University of Utah, as a research associate investigating the role of hepatic toxicants on liver metabolism in lab animals. In 1994, Dr. Ho was appointed lecturer in the Department of Biochemistry and, in 2005, he was appointed associate professor at The Chinese University of Hong Kong and became an instrumental part of the toxicology programme in the School of Life Sciences.

Dr. Ho holds memberships in several professional associations, including the United States Society of Toxicology, the American Chemical Society, the New York Academy of Sciences, the American Institute of Chemists (fellow), and the Protein Society. He has been appointed a consultant scientist by professional groups and the local government, including Government Secretariat Home Affairs Bureau and the HK Chemical Waste Association.

Dr. Ho's work has been supported in part by the university research grants from the Hong Kong Higher Education and Innovation and Technology Commission and the Croucher foundation. He has received awards from the American Society for Biochemistry and Molecular Biology for students' papers.

Dr. Ho has authored and coauthored approximately 100 papers and proceedings in peer-reviewed international journals and holds patents on herbal medicines. He has contributed original data to the Protein Data Bank (PDB) and has applied for patents under the Patent Cooperation Treaty (PCT) for anticancer agents in the United States. He lectures regularly on toxicology to undergraduate, and graduate students. Dr. Ho continues to perform fundamental research on the cytotoxic effects of environmental and food chemicals and the development of therapeutic agents on cultured human cells and animal models.

Abbreviations

Abbreviations	Terms
ADME	Absorption, distribution, metabolism, and excretion
AML	Acute myeloid leukemia
BM	*Bacopa monnieri*
CAM	Complementary and alternative medicine
CAT	Catalase
CI	Combination index
CIA	Collagen-induced arthritis
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
CRS	Chemical reference substances
DHA	Dihydroartemisinin
EBV-EA	Epstein-Barr virus early antigen
ER	Estrogen receptor
ERS	Extractive reference substance
FAHF	Food allergy herbal formula
GA	Gambogic acid
GABAA	Gamma-aminobutyric acid (Type A)
GSK3	Glycogen synthase 3 kinase
GT	Gallotannin
H1	Histamine type 1 receptor
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High density lipoprotein
^{1}H NMR	Proton nuclear magnetic resonance
HO-1	Heme oxygenase-1
HSCs	Hepatocyte stellate cells
ICA	Independent component analysis
IKK	I kappa B kinase
IL	Interleukin
Iso-GNA	Isogambogenic acid
KPS	Karnofsky performance score
LCAT	Lecithin cholesterol acyltransferase
LDH	Lactate dehydrogenase
LPL	Lipoprotein lipase
MDR	Multidrug resistance
MFAX	Methanol fraction of amomum xanthoides

NF	Nuclear factor
NIH	National Institutes of Health
NSAID	Nonsteroid anti-inflammatory drug
PBMC	Peripheral blood mononuclear cells
PCA	Principal component analysis
PCNA	Proliferating cell nuclear antigen
PDE5	Phosphodiesterase (Type 5)
PI3K	Phosphatidylinositol-3-kinase
PKC	Protein kinase C
PMA	Phorbol myristate acetate
PPARs	Peroxisome proliferator-activated receptors
PTEN	Phosphatase and tensin homologue
PXR	Pregnane X receptor
RA	Rheumatoid arthritis
ROS	Reactive oxygen species
RR	Relative risk
RTKs	Receptor typosine kinases
SOD1	Superoxide dismutase 1
Tan I	Tanshinone I
TCE	Trichloroethylene
TCM	Traditional Chinese medicine
THL	Tien–Hsien Liquid
TI	Therapeutic index
TLBZT	Teng-Long-Bu-Zhong-Tang
TNF	Tumor necrosis factor
UGTs	UDP-glucuronosyltransferases
VEGF	Vascular endothelial growth factor

1 Introduction

There is an increasing use of herbal medicines for the treatment of various ailments worldwide. Herbal medicines are often taken in combination with other therapeutic drugs in China and other Asian countries. For thousands of years, specific herbal formulations have been used for the treatment of various diseases in China. It is believed that individual herbs in the formulations would act on different targets and systems to produce the expected health benefits. However, the combination of herbs with therapeutic drugs can raise potential health risk. The health risk is probably attributed to drug–herbal interactions. Data from human studies indicate that *Hypericum perforatum*, also known as St. John's wort, decreased the blood concentrations of amitriptyline, warfarin, and theophylline, whereas it did not alter the pharmacokinetics of dextromethorphan, mycophenolic acid, and pravastatin [1]. *H. perforatum* also decreased the plasma concentration of the active metabolite SN-38 in cancer patients after irinotecan treatment. Both pharmacokinetics and pharmacodynamics are believed to be affected by drugs–herbal interactions. The potential interactions of herbal active ingredients with drugs are of a major concern in the combination therapy. Administration of drugs and herbal medicines requires appropriate strategy in order to reduce potential herb–drug interactions, and to enhance herbal safety and efficacy.

HERBAL MEDICINES AS COMPLEMENTARY MEDICINE FOR CANCER THERAPY

In Chinese medicine, mortal damage is a consequence of the disorientation and imbalance of "Yin-Yang," which helps human beings try to sustain harmony and integrity. Cancers and tumors are the consequence of unmitigated accumulations of "qi," moisture, and blood that have intoxicated the system [2]. These factors are transformed into morbid tissue, obstructing the normal circulation of blood and lymph. Consequently, it leads to depletion of "qi" and blood resulting in a deregulation of growth typical of cancer. Therefore, treatment that supplements "qi," moisture, and blood can restore circulation and alternates stasis. This can replenish the essence that governs growth and maturation and repair mechanism.

It is believed that the relationship between generating blood and its circulation is meant to prevent both deficiency and stagnation. The blood flows to every part of the body and moistens and lubricates all the tissues.

When there is insufficient "ying qi," the distribution of "qi" is significantly interrupted. Consequently, therapeutic measures are administered to remove the obstruction and generate new blood. Chinese herbs such as angelica, salvia, and millettia can be used to treat both deficiency and stasis because they can enhance blood circulation.

Cancer patterns involve accumulation of carcinogenic metabolites, deficient "qi" and blood, and blood stagnation. For example, stomach cancer may result from various patterns such as liver "qi" invading the stomach, stomach "yang" deficiency, phlegm stagnation and blood stagnation due to "qi" stagnation, stomach "yin" deficiency due to stomach heat, and "qi" and blood deficiency. Depending on the patterns of deficiency, herbal therapies are individualized to fit different patients according to the pathological patterns and the health status of the patient. Herbal formulas relieve stagnation by using "qi-" and blood-activating herbs and antidote toxins. Anticancer herbs can remove or dissolve these pathogenic entities.

There are many treatment strategies that combine acupuncture and Chinese medicines to reduce toxins and enhance the reduced circulation, both of which are caused by tumors, cancers, and the adverse effects of surgery, radiation, and chemotherapy. Herbal formulas are especially effective in invigorating the "qi," nourishing the blood, and clearing the system. Herbal medicines can enhance adaptation to stress and increase host defense mechanism, which will increase resistance to inflammation and infection and suppress the progression of tumors. Consequently, herbal medicines can extend life span of patients. These are primary therapeutic protocols for the management of cancer in China and some other Asian countries. Chinese herbal medicine represents complementary or adjunctive therapies that often can improve the efficacy of Western medicine to achieve the pharmacological effects.

The signs and symptoms of deficiency of "qi," moisture, and blood manifest themselves as the adverse effects of radiation and chemotherapy. Replenishing these deficiencies of "qi," moisture, and blood require medication. Herbal medicines become the top choice especially in generating these resources in the system. While Western medicine aggressively inhibits the cancer, yet, with side effects, traditional Chinese medicine supports and restores the functions of vital organs that enable patients to recover slowly from conventional therapies. The quality of life of patients can be improved.

MODERN CHINESE HERBAL RESEARCH

With the advent of science and biotechnology, clinical researchers worldwide, especially from China and Japan, have begun searching for ways to improve treatment strategy in combination with herbal medicine.

Over the last decades, this approach has become known as Fuzheng Gu Ben therapy, which is meant to strengthen the existing health status and secure the root. Fuzheng herbs support nonspecific resistance and are also known as adaptogens. It is believed that patients with advanced malignant tumors usually show symptoms of deficiency in "qi," blood, liver, and kidney, as well as dysfunction of spleen and stomach. Tonics may improve the general health condition and the immune function [3]. Tonic treatment benefits the treatment of cancer patients. Fuzheng therapy produces diverse biologic effects that include the following:

1. Reduction of tumor mass
2. Suppression of the formation of a new primary cancer
3. Enhancement of the immune function
4. Bolstering of the regulatory function of the endocrine system
5. Protection of the structure and function of internal organs and glands
6. Strengthening of the digestive system by improving absorption and metabolism
7. Protection of the bone marrow and hematopoietic function
8. Treatment of adverse side effects due to drug toxicity

A couple of excellent resources on the role of Chinese herbs in cancer therapy is *Cancer and Natural Medicine* and *Natural Compounds in Cancer Therapy*, which are authored by John Boik [4,5].

Herbal medicines have become increasingly popular among cancer patients. They often use herbal medicines as adjuvant therapy to reduce the side effects of the common chemotherapy. However, interactions between herbal medicines and cancer drugs can occur if administered inappropriately. These herb–cancer drug interactions can reduce the efficacy of cancer drugs and cause adverse consequences for cancer patients. Adverse interactions between herbal medicines and therapeutic drugs have been reported. The herb–drug interactions are involved with drug-metabolizing enzyme system. Extracts of *Oldenlandia diffusa* and *Astragalus propinquus* were reported to inhibit CYP3A4 in human [6]; these herbs significantly induced human pregnane X receptor (PXR)-mediated CYP3A4. Concomitant use of *O. diffusa* and *Rehmannia glutinosa* resulted in the induction of CYP3A4 and consequently reduced the efficacy of drugs. Herb–drug interactions between herbal medicines and CYP3A4 substrates can occur.

Despite potential health risk associated with herb–cancer drugs interactions, cancer patients always take herbal supplements in order to reduce cytotoxicity of cancer drugs. In women with advanced breast cancer, coadministration of garlic supplement reduced the clearance of docetaxel [7].

The study did not alleviate cancer drugs–induced hematological toxicity, but alternate drug–induced nausea. Most cancer drugs are substrates of P-glycoprotein and can cause multidrug resistance (MDR)–associated proteins and other transporters [7]. Induction and inhibition of the drug-metabolizing enzymes and transporters may affect efficacy of therapeutic drugs. Therefore, the selection of appropriate herbal medicines and the cancer drug for cancer therapy is important to avoid health hazard.

HEALTH BENEFITS OF HERBAL MEDICINES

A large number of herbal medicines are used for treating cancer or reducing the cytotoxicity of chemotherapeutic drugs. Some of the herbal medicines have been reported to show health effects on cancer and attenuate therapeutic drugs–induced toxicities. However, there is not much clinical data associated with the use of herbal medicines in cancer therapy. A survey has identified herb–chemotherapeutic drug combinations in the selected group of cancer patients [8]. Among 42 cancer patients using herbal medicinal remedies in combination with chemotherapy, 47 different potential herb–drug interactions were identified on the level of cytochrome P-450 metabolizing enzymes and glycoprotein transport in vitro. Common herbal remedies included garlic, ginger, and green tea. The clinical potential for cytochrome P-450 metabolizing enzyme interactions in humans was reported for green tea and echinacea. The study reported that garlic displayed strong interactions with glycoprotein. In addition, the use of food supplements including practice among cancer patients. The concurrent use of complementary medicine and natural health products with therapeutic drugs may reduce the efficacy of radiotherapy as well.

Although conventional treatments with cancer drugs can extend the life of cancer patients, the adverse side effects of these cancer drugs pose a limitation to cancer therapy. The cytotoxicity causes significant psychological and spiritual stress in cancer patients. Neither herbal medicines nor Western medicine alone can satisfactorily alleviate the stress associated with therapeutic drugs. Herbal medicine modalities offer less toxicity; yet, effective treatment for advanced cancers remains to be investigated. A combination of Western medicine and herbal medicines would complement each other for the treatment of cancer. Health risks of integrating herbal medicines with cancer drugs can be ameliorated. An integrative approach can harness the strengths of Western medicine and herbal medicine [9].

Cancer and the related complications significantly compromise immune response and the quality of life. The pharmacological effects of herbal medicines such as anticancer medicines or adjuvants can increase the cancer drug efficacy and ameliorate undesirable side effects of cancer drugs.

The combination of drugs and herbal medicines revealed that the antitumor immunity can be improved [10].

HERBAL MEDICINES AS A RICH SOURCE FOR DRUG DEVELOPMENT

Herbal medicine has become a rich source of anticancer agents and facilitates the development of efficacious cancer drugs. However, extensive screening tests of the potential active phytochemicals in vitro are needed. In vitro combination and characterization of potential anticancer phytochemicals against human cancer cell lines are commonly performed. Potentially effective combinations of beta-elemene with taxanes were explored and demonstrated in human lung cancer cells [11]. Synergistic interactions were observed with combinations of ss-elemene and taxanes. This is related to the enhanced cytotoxicity of taxanes via induction of cytochrome c release from mitochondria, caspase-8, and -3 cleavage and downregulation of Bcl-2 and Bcl-X-L expression. The anticancer activity of the combination of herbal medicines and cancer drugs has raised tremendous interest worldwide.

The health benefits of herbal medicines are attributed to the synergistic interactions with anticancer compounds. This combination strategy for the treatment of cancer is used to evaluate the composition of traditional Chinese medicine formulation. Yanhusuo San consisting of Rhizoma Corydalis and Rhizoma Curcumae was an ancient Chinese medicine prescription for the treatment of cancer dated back in AD 960–1279 [12]. A common approach is to compare the IC_{50} of each herbal extract and both extracts at different compositions by MTT assay. The isobologram and combination index (CI) are used to evaluate the synergistic effects of the herbal extracts. Flow cytometry, fluorescence analysis, Western blot analysis, and gene expression profile can be used to fathom out the mechanism of actions of the herbal extracts. A plausible molecular mechanism of the synergistic antitumor effects of Rhizoma Corydalis and Rhizoma Curcumae was reported [11].

ACTIVITY-BASED FRACTIONATION OF HERBAL EXTRACTS

The active fractions are derived from the activity-based fractionation of herbal extracts in in vitro and in vivo study. However, the antitumor activity of single phytochemicals may not show effects in animal study. Nevertheless, the composition of phytochemicals with antitumor effects in cancer cell lines can be evaluated in vivo. *Curcuma aromatica* and *Polygonum cuspidatum* are widely used herbs for liver cancer therapy. Curcumin, the active principle of *C.aromatica*, and resveratrol, the active

principle of *P. cuspidatum*, contribute to the anticancer effects in colon cancer [13]. The combination of curcumin and resveratrol significantly inhibited the proliferation of Hepa-1-6 cells. The combination of phytochemicals may enhance the efficacy of herbal medicine. The combination of curcumin and resveratrol is a good example of combination strategy for liver cancer treatment.

Current data basis of herbal medicine is limited. Bioinformatics on the selection and synergism of herbal extracts and constituents with anticancer properties are warranted to be developed. Chemoinformatics methodology can play an important role in clinical applications and are helpful in drug development. Novel herbal extract in combination of cancer drugs were characterized in ACHN and A2780/cp cells with chemobioinformatics-aided analysis [14]. Chemobioinformatics confirmed the predicted outcomes. It could provide useful information on the use of herbs in reversing MDR.

Herbal medicines are commonly used in food supplement for improving general health. Diet is not the primary therapy for refractory forms of cancer. Yet an appropriate food supplement may be effective as an adjuvant to hormone deprivation therapy for cancer. This treatment strategy could delay relapse and inhibit refractory growth. Zyflamend, a combination of multiple herbal extracts, was reported to exhibit anticancer properties [15,16]. Zyflamend can inhibit growth of various prostate cancer cell lines and androgen-dependent tumor growth in a mouse model at the advanced stages of prostate cancer. Herbal extracts as adjuvant in food supplements have become a common approach in cancer therapy. The active herbal extracts also exhibit chemoprotective properties against carcinogenesis.

Herbal medicines generally show health benefits toward different types of cancer. They have been used as complementary and alternative medicine for different cancer therapies. Although herbal medicines may take a longer period of time to show pharmacological effects in cancer patients, the adverse side effects of herbal medicines are minimal. Often, herbal formulations are preferred based on clinical practices. Teng-Long-Bu-Zhong-Tang (TLBZT) was demonstrated to show anticancer effects on colorectal cancer in vitro [17]. TLBZT significantly inhibited CT26 colon carcinoma growth via apoptotic caspase cascade. It can enhance the anticancer effects of 5-Fu in CT26 colon carcinoma.

Herbal medicines are known to be able to enhance the efficacy of cancer drugs. A combination of the active constituents can be more effective anticancer agents. A combination of Jaceosidin, emodin, and magnolol showed remarkable anticancer activities in melanoma A375 [18]. The combination of these phytochemicals induced cell cycle arrest and, consequently, apoptosis in melanoma A375 cell line. However, a different combination of emodin with magnolol was more effective than the other combinations.

TRADITIONAL HERBAL FORMULATIONS

Traditional herbal formulations represent specific composition of herbal extracts prepared in boiling water. However, it is realized that temperature effect may have a significant impact on extraction efficiency and stability of phytochemicals [19,20]. The chemical properties of chlorogenic acid, an active component in green tea and traditional Chinese medicine, can be changed through boiling, yet, the anticancer properties of chlorogenic acid and its derivatives remained the same against CCl_4-induced toxicity in hepG2 cells [19]. Herbal extraction of *Scutellaria baicalensis* Georgi, *Glycyrrhiza uralensis* Fisch, *Paeonia lactiflora* Pall, and *Ziziphus jujuba* Mill in boiling water enhanced the anticancer activities of chemotherapy in various cancers in various mouse tumor xenograft and allograft models [20].

CLINICAL EVALUATION OF HERBAL MEDICINES

Laboratory studies of herbal medicines are expanding the clinical knowledge. Different herbal extracts can be prepared as natural health products. Specific formulations are more effective to target molecular pathways, including angiogenesis and epidermal growth factor receptor, which plays a significant role in cancer growth. Quality assurance of specific herbal extracts is important as herbs obtained from different geographical regions might not have the same anticancer properties. Their effectiveness may be affected when multiple herbal agents are used. An integrative approach for managing cancer should target the multiple signaling pathways associated with cancer growth. Angiogenesis is an essential process in cancer development. Herbal products can affect angiogenesis and consequently inhibit cancer growth [21]; thus, herbal extracts with antiangiogenic activity may be good anticancer agents. Examples of antiangiogenic herbs include *Artemisia annua*, *Viscum album*, *Curcuma longa*, *S. baicalensis*, *Magnolia officinalis*, *Camellia sinensis*, *Ginkgo biloba*, *Panax ginseng*, and quercetin. Surprisingly, other active phytochemicals may not show high anticancer effects when used alone, yet they can interact with other components in the herbal extracts to produce anticancer activities. Baicalin, an active phytochemical with antipyretic properties, in combination with *Salvia miltiorrhiza* or *C. sinensis* extracts showed antiproliferation effects on the human breast cancer cell lines MCF-7 and T-47D [22]. The combination of active compounds from different classes offers either enhanced therapeutic benefits or antiproliferative effects on tumor growth. The antiproliferative effects of these compounds can be extended to other cancer types, suggesting that these compounds in combination with herbal extracts may function through different mechanisms. The advantages of

using herbal medicines in cancer therapy are demonstrated in different studies either in combination with cancer drugs or in combination with other herbal extracts.

Increasing failure rates with cancer chemotherapy, the high cost, and limited drug efficacy have prompted alternative approaches to cancer treatment and drug discovery. Common molecular basis of cancer biology has been discovered through advancements in genomics and proteomics. With the advent of biotechnologies, a large numbers of potential drug candidates can be tested against a particular molecular target; thus, novel cancer drugs derived from herbal principles can be developed. One of the most abundant natural sources for active compounds is herbal medicines. Natural products and their derivatives have been purified and structurally identified from herbal medicines. These active phytochemicals exhibit immense pharmacological and anticancer properties. Although the molecular mechanism of actions of active anticancer phytochemicals are yet to be elucidated, extensive research in herbal medicine continues to generate new data that are worth further investigation in clinical testing. Recent advancement in biotechnology and chemical technology has enabled us to understand the salient interactions of natural products and their derivatives with cancer cells. As a result, the findings allow us to better design cancer drugs. Both the natural products and synthetic molecules share high chemical selectivity and pharmacological specificity. The ability of novel natural products to interact with specific protein domains would trigger a chain of cellular signaling processes. By virtue of specific binding affinity to gene products, natural products can provide effective scaffolds for the pharmacological processes [23]. Potent natural products should show properties specified in the "Lipinski's rule of five" [24]. The application of bioinformatics to quality control and the efficacy of natural product derivatives, in particular small natural molecules, should be used to enhance the interactions with molecular targets. However, these small naturally occurring products may involve multiple cellular targets and pathways. The inhibition of multiple mechanistic pathways may ameliorate chemoresistance in various cancers. Table 1.1 shows the anticancer properties of active phytochemicals and their mechanism of actions. A better understanding of the interactions between natural compounds and the derivatives in cancer cells is pivotal for the development of targeted anticancer agents. The discovery and development of potent anticancer agents from herbal medicines is hampered by lack of preclinical model for the evaluation of the potency of anticancer phytochemicals. However, xenograft models and transgenetic models can serve as surrogates in developing therapeutic anticancer drugs. Nevertheless, these models can show significant biochemical and physiological difference from humans. One of the potential issues associated with animal models for evaluation of potential drug efficacy is inappropriate dosing. With the

TABLE 1.1
Anticancer Activities of Active Phytochemicals

Herbal Compound	Specialty	References
Berberine	1. Completely antagonizes the TNF alpha-mediated barrier defects in the cell model 2. Dysregulation of protein folding, proteolysis, redox regulation, protein trafficking, cell signaling, electron transport, metabolism, and centrosomal structure in breast cancer cells	[26,27]
Baicalein	1. Inhibits the invasion of MDA-MB-231 human breast cancer cells 2. Inhibits tumor cell invasion and metastasis by reducing cell motility and migration via the suppression of the extracellular signal-regulated kinases (ERK) pathway	[28,29]
Rocaglamide	1. Sensitizes CD95L- and TRAIL-induced apoptosis in HTLV-1-infected cells by downregulation of c-FLIP expression 2. Blocks DNA damage-induced upregulation of the transcription factor p53 by inhibiting its protein synthesis	[30,31]
Shikonin	Inhibits tumor cell growth in estrogen receptor alpha (ER alpha)-positive, but not ER alpha-negative breast cancer cells	[32]
Rhein	Dysregulation of cytoskeleton regulation, protein folding, glycolysis pathway, and transcription control in breast cancer cells	[33]
Silymarin	1. Membrane-stabilizing and antioxidant activity promotes hepatocyte regeneration 2. Reduces the inflammatory reaction, inhibits the fibrogenesis in the liver	[34,35]
Catechin hydrate	Antiproliferative effects of CH in the prevention of cervical cancer	[36]
Ursolic and oleanolic acids	1. Upregulates p53 expression and inhibits breast cancer cell growth 2. Exerts antiproliferative and apoptotic effects selectively in ERa-positive breast cancer cells	[37]
Tanshinone I (Tan I)	Induction of apoptosis by Tan I in leukemia cells	[38]
Dihydroartemisinin (DHA)	Induces cell apoptosis by triggering reactive oxygen species (ROS)-mediated caspase-8/Bid activation and the mitochondrial pathway	[39]

(*Continued*)

TABLE 1.1 (*Continued*)
Anticancer Activities of Active Phytochemicals

Herbal Compound	Specialty	References
Gallotannin (GT)	Downregulates the expression of NF kappa B-regulated inflammatory cytokines (IL-8, TNF alpha, IL-1 alpha) and caused cell cycle arrest and accumulation of cells in pre-G(1) phase	[40]
Oridonin	Apoptosis- and autophagy-inducing activity in cancer therapy	[41]
Fei-Liu-Ping ointment	Reduces the concentration of serum proinflammatory cytokines IL-6, TNF-[alpha], and IL-1[beta]	[42]
Isogambogenic acid (iso-GNA)	Inhibits tumor angiogenesis	[43]

improvement of animal models for human tumors at different developing stages, anticancer activities of potent phytochemicals that are identified from herbal extracts are likely to be helpful in drug development [25].

Identification of specific biomarkers in cancer therapeutics is essential for the comparison of efficacy of potential phytochemicals from herbal extracts. Bioinformatics on different biological systems offers useful information related to molecular signaling activity and assays for cancer biomarkers.

The use of herbal formulation for cancer therapy depends on the documented ancient formula and the quality of herbs that can vary significantly in phytochemical contents and anticancer properties due to geographical differences in herbal medicines. This has hampered the clinical use of ancient herbal formulation for the treatment of cancer. Establishment of a useful relationship between a potent anticancer photochemical and cancer remains a challenge. Although cancer biology has been helpful in fathoming out the pathogenesis, only a limited number of the preventive measures based on herbal medicines are successful in human. However, herbal medicines remain one of the rich resources of anticancer agents for novel drug development. A combination strategy with cancer drugs and herbal medicines should be established for cancer therapy.

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TABLE 1.1 (Continued)

Anticancer Activities of Active Phytochemicals

Herbal

Gallotannin (GT) Downregulates the expression of NF kappa B-regulated in□ammatory cytokines (IL-8, TNF alpha, IL-1 alpha) and caused cell cycle arrest and accumulation of cells in pre-G(1) phase [40]

Oridonin Apoptosis- and autophagy-inducing activity in cancer therapy [41]

Fei-Liu-Ping

ointment Reduces the concentration of serum proin□ammatory cytokines IL-6, TNF-[alpha], and IL-1[beta] [42]

Isogambogenic

acid (iso-GNA) Inhibits tumor angiogenesis [43]

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4 Chapter 4: Plant-Derived Active Phytochemicals Show Various Biologic and Pharmacological Activities in Cancer

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6 Chapter 6: Mechanism of Cancer Drug Action

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9 Chapter 9: Exploration of Herbal Medicine

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