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Molecular and Cellular Mechanism Studies on Anticancer Effects of Chinese Medicine

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1. Introduction

Chinese medicine is an unique medical system, among which Chinese medicines (including Chinese medicinal plants, Chinese animal drugs, Chinese mineral drugs and composite formulae) have been used in main stream medical health care in China for years of thousands and have been accepted by many countries as complemental and alternative medicine. As one of the major traditional medicines and Ethnomedicines in the world, Chinese medicines as a resource and materials for unmet medical needs have been attracted by scientists in medical, pharmaceutical, biomedical engineering and life sciences. The challenges in safety (such as Aristolochic acid nephropathy, Chinese medicines adverse reaction and herb-drug interaction), quality control (like batch-to-batch reliable, contamination pesticide and heavy metals) and green environments (protection of endangerous species from animal and plants) have also become emerging issues. In the past decades, chemical and pharmacological profiles of many Chinese medicines have been extensively studied. In this chapter, we focus on advanced progress in molecular and cellular mechanism studies on anticancer action of Chinese medicines by trend prediction from top journals of Chinese medicine, ethnomedicines, alternative and complemental medicine. 12 representative Chinese medicines were selected in this chapter (Rhizoma coptidis, arsenic, Rhizoma Curcuma longae, Radis stephaniae tetrandrae, Radix tripterigii wilfordii, Radix scutellariae, Herba artemisiae annuae, Radix ginseng, Radix notoginseng, Radix astragali, Radix angelicae senensis and Radix salviae miltiorrhizae) and we reviewed the recent progress in order to understand their pharmacological action, active chemical ingredients and application of new approaches (genomics, proteomics and metabolics). We concentrated on the cellular and molecular mechanisms of the therapeutic actions of these Chinese medicines and introduced the major active chemical ingredients in relation to therapeutic values. These Chinese medicines can be used in treatment of cancer. After reviewing hot Chinese medicines in treatment of cancer in this chapter, we hope it will lead to further exploration of Chinese medicines by advanced scientific technology in drug discovery for treating cancer.

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2. Important

This chapter reviewed the recent progress on Chinese medicines in the cellular and molecular mechanism studies and the major active chemical ingredients of Chinese medicines in relation to therapeutic values in order to understand their pharmacological action, active chemical ingredients and application of new approaches. We noted that the cellular and molecular mechanisms and the major active chemical ingredients of Chinese medicines have been deeply and widely studied which provide a useful information for new drug development and Chinese medicine clinical practice, but the challenges in safety (such as Aristolochic acid nephropathy, Chinese medicines adverse reaction and herb-drug interaction), quality control (like batch-to-batch reliable, contamination pesticide and heavy metals) and green environments (protection of endangered species from animal and plants) have also become emerging issues. On the other hand, research mainly focused on single Chinese medicines in the past decades, we should do more studies on composite formulae (consist of over two single Chinese medicines) by using new technologies, such as “Omics” technologics and system biology to get more evidences for Chinese medicine practice and new drug development in the future.

3. The structure of this chapter

The selected twelve Chinese medicines cover the following contents:

i. Name of the herb: Common names, botanical name, family, origin, distribution, commercially cultivated or wild, traditional use in Chinese medicine clinical practice

ii. General chemical and pharmacological profiles

iii. Mechanism studies on anticancer effect of Chinese medicines in in vitro and in vivo study

iv. Adverse reactions

v. References

4. The contents of this chapter

4.1 Rhizoma coptidis (Huanglian in Chinese)

Coptis Rhizome (CR) is the dried rhizome of Coptis chinensis Franch (Ranunculaceae). Its Chinese name is huanglian, which was first recorded in Shen Nong Ben Cao Jing (Shen Nong’s Materia Medica, 220 A.D.) Other two species of Coptis Rhizome (Coptis deltoidea C. Y. Cheng et Hsiao. and Coptis teetoides C. Y. Cheng (or Coptis teeta Wall.) were also specified in the Chinese Pharmacopoeia (The State Pharmacopoeia Commission of the P.R. China, 2005). It is native to Sichuan, Hubei, Xizang, Shanxi, and Jiangxi Province of China. The source of Huanglian can be obtained from wild species of or cultivated plants. The GAP base of Huanglian in China is located in Chongqing, Hubei. Traditionally, CR can be used in treatment of diseases like diarrhea, inflammation of the eye, and women’s abdomen ailments caused by damp-heat.

Raw material of CR mainly includes a series of alkaloids, such as berberine, coptisine, epiberberine, berberrubine, palmatine, columbamine, jarorrhizine, worenine, magnoflorine, groelandicine, berberastine, oxyberberine and thalifendine etc. Other chemicals in CR include ferulic acid, obakunone and obakulactone etc. Berberine is the main component and is credited as criteria for quality control of CR in China Pharmacopoeia (Edition 2005). CR and berberine have been used for treatment of intestinal infections (acute gastroenteritis,
cholera and bacterial diarrhea) by their antibacterial and antiviral effects, treatment of hypercholesterolemic patients and type 2 diabetes by hypolipidemic effects, and various experimental heart diseases, such as heart failure, cardiac dysfunction, pressure-overload induced cardiac hypertrophy (Feng et al., 2010). Berberine may help in neuropsychiatric diseases by inhibiting Prolylligopeptidase, a peptidase associated to schizophrenia, bipolar affective disorder and related conditions (Tarrago et al., 2007).

Recently, the most attractive pharmacological effect of CR and berberine is its anticancer activities (Tang et al., 2009). CR and berberine were used for prevention and treatment of human cancers, such as nasopharyngeal carcinoma (NPC), cholangiocarcinoma with complication of liver cancer, and phase I study of CR (Chinese Herb) in patients with advanced solid tumors (Tian et al., 2000; Feng et al., 2008; http://cancer.gov/clinicaltrials/MSKCC-00061). Berberine is the principal active compound of anticancer effect in CR (Hara et al., 2005). There are many reports showing that berberine could inhibit proliferation of cancer cells in gastric cancer, leukemia, melanoma, liver cancer, colorectal cancer, pancreas cancer, oral cancer, breast cancer, cervical cancer, lung cancer, NPC and prostate cancer cell line models and may have potential chemotherapeutic properties against human cancers (Lin et al., 2006; Jantova et al., 2003; Serafim et al., 2008; Piyanuch et al., 2007; Katiyar et al., 2009; Lin et al., 2004; Lee et al., 2006; Liu et al., 2005; Kim et al., 2004). Current studies broadly indicate the involvement of cell cytotoxicity, cell cycle regulatory machinery, inflammation and cell death signalling pathways as targets of anticancer by berberine and Huanglian. It was demonstrated that CR extract can inhibit cancer cell growth by suppressing the expression of cyclin B1 and inhibiting CDC2 kinase activity in human cancer cells and induce apoptosis by up-regulation of interferon-beta and TNF-alpha (Low et al., 2002; Li et al., 2000; Kang et al., 2005). Multiple mechanisms underlying the anti-cancer action of CR and berberine have been reported and may involved inhibition of NFkappa-b pathways, induction of cell cycle arrest and apoptosis (Pandey et al., 2008; Hsu et al., 2007; Mantena et al., 2006). Anti-metastatic effects of berberine have been reported and inhibition of urokinase-plasminogen activator and matrix metalloproteinase-2 was implicated (Peng et al., 2006). It was also reported that berberine inhibits HIF-1alpha expression via enhanced proteolysis (Lin et al., 2004). Anti-inflammation may be another profile of CR and berberine in treatment of Cancers. The anti-inflammatory efficacy of berberine is due to its inhibition of prostaglandin E2 (PGE2) followed by the reduction of COX-2 protein in vivo and in vitro of malignant tumor (Kuo et al., 2004). Berberine could suppress inflammatory agents-induced interleukin-1beta (IL-1beta) and Tumor necrosis factor-alpha (TNF-alpha) productions via inhibiting the phosphorylation and degradation of inhibitor of kappa B-alpha (IkB-alpha) (Lee et al., 2007). We provide a new mechanism for anti-invasion of berberine which is to inhibit RhoA signaling pathway, an upstream of NF-kappa B (Tsang et al., 2009). In this study, we found that berberine distribution in cell nuclear and cytoplasm in dose dependent manner, so anti-invasion of berberine may inhibit RhoA signaling pathway at low dose while apoptosis are induced by berberine via G2 arrest at high dose in NPC cell lines. Furthermore, at low dose, we use liver cancer cell lines (MHCC97-L) to demonstrate that CR extract has better anti-invasion than berberine and clarify that anti-invasive effect of CR extract on MHCC97-L cell line specific acts on F-actin via Rho/ROCK signaling pathway, but not other metastasis-related molecules such as integrin beta4, E-cadherine, u-PA and MMPs (Wang et al., 2010). At high dose, we use liver cancer cell lines (MHCC97-L and HepG2) to demonstrate that berberine can induce both apoptotic and autophagic cell death, in which apoptosis is major cell death type (Wang et
Our results suggest that CR and berberine are promising alternative therapies in the treatment of cancers. Computer-aided molecular design and prediction of cell responses to CR, berberine, and analogs, along with genomics and proteomics, microRNA approaches to study antineoplastic effects of berberine and Huanglian are expected in the future. The relatively low toxicities at therapeutic levels for both Huanglian and berberine also show additional benefits for their further development.

Adverse responses of berberine include constipation, laxative, anaphylaxis and other skin allergies such as dermatitis and rashes, and overdose may cause respiratory and circulatory system problems (Bao, 1983). Furthermore, berberine could displace bilirubin from serum-binding proteins, causing jaundice, kernicterus, and brain damage in infants (Bateman et al., 1998; Chan, 1993, 1994).

4.2 Arsenic (Pishuang in Chinese)
In Chinese medicine, arsenic was first recorded in Chinese book “KAI BAO BAN CAO” (Kai Bao of Materia Medica, 973 A.D.). Arsenic has various forms. The most important compounds of arsenic are arsenic trioxide, As2O3, (“white arsenic”), the yellow sulfide orpiment (As2S3) and red realgar (As2S2). In 2006 and 2007, China was the top producer of arsenic trioxide with almost 50% world share, followed by Chile, Morocco and Peru, reports the United States Geological Survey [U.S. Geological Survey, 2008]. In modern society, arsenic and its compounds are used as pesticides, herbicides, insecticides and in various alloys, while arsenic compounds used as anti-cancer agents are a fascinating story. Arsenic has a long history of use in Chinese and Western medicine for cancer treatment. Contemporary clinical use of arsenic trioxide is largely due to purification of this compound from traditional mixtures, and the definition of effective, low-dose regimens for the treatment of acute promyelocytic leukemia (APL) [Chen et al., 2002].

In the 90’s years of last century, two arsenic components including arsenic trioxide (As203) [Sun et al., 1992] and arsenic disulfide [Huang et al., 1995] used in some traditional Chinese formulae have been shown very effective in patients with acute promyelocytic leukemia (APL) treatment. Using NB4 cells model, cellular and molecular mechanisms of arsenic trioxide treatment have been clarified by modulation of bcl-2, as well as PML-RAR alpha and/or PML proteins and induction of apoptosis, which is independent from the retinoid pathway [Chen et al., 1996]. Further studies indicated that As2O3 had dose-dependent dual effects on APL cells: inducing preferentially apoptosis at relatively high concentrations (0.5 to 2 micromol/L) and inducing partial differentiation at low concentrations (0.1 to 0.5 micromol/L) [Chen et al., 1997], and As2O3 treatment is also an effective and relatively safe drug in APL patients refractory to all-trans retinoic acid (ATRA) and conventional chemotherapy [Shen et al., 1997]. Differentiation and apoptosis induction therapy in APL was established by combination therapy of ATRA and As2O3 [Giannì et al., 1998; Wang et al., 2000]. Synergic effects of arsenic trioxide and other drugs on APL, chronic myeloid leukemia and other solid cancers, such as in patients with primary hepatocellular and gallbladder tumors were also recommended [Chen et al., 2002; Du et al., 2006; Wang et al., 2008; Hu et al., 2009]. PML and PML-RARalpha (a fusion protein containing sequences from the PML zinc finger protein and retinoic acid receptor alpha) degradation is triggered by their SUMOylation, but the mechanism by which arsenic trioxide induces this posttranslational modification is unclear. Recently, Chen’s group reported in Science demonstrated that PML is a direct target of arsenic trioxide providing new insights into the...
drug’s mechanism of action and its specificity for APL. They showed that arsenic binds directly to cysteine residues in zinc fingers located within the RBCC domain of PML-RAR and PML. Arsenic binding induces PML oligomerization, which increases its interaction with the small ubiquitin-like protein modifier (SUMO)-conjugating enzyme UBC9, resulting in enhanced SUMOylation and degradation [Zhang et al., 2010].

Arsenic and many of its compounds are potent poisons. The International Agency for Research on Cancer (IARC) recognizes arsenic and arsenic compounds as group 1 carcinogens, as their toxic mechanisms, arsenic disrupts ATP production through several pathways [Klaassen C, Watkins J. 2003].

Arsenic is known to cause arsenicosis owing to its manifestation in drinking water. The study of chemolithoautotrophic As(III) oxidizers and the heterotrophic As(V) reducers can help the understanding of the oxidation and/or reduction of arsenic [Croal et al., 2004]. Treatment of chronic arsenic poisoning has been accomplished [The Psychiatric, Psychogenic and Somatopsychic Disorders Handbook. 1978].

4.3 Rhizoma Curcumae longae (Jiang Huang in Chinese)

Rhizoma Curcumae longae is the dried rhizome of Curcuma longa L. (Zingiberaceae), mainly produced in Sichuan, Fujian, Jiangxi and Yunnan. It was first recorded in Xin Xiu Ben cao (659 A.D.). The rhizome is collected in autumn and winter when the aerial part wither, washed clean, boiled or steamed thoroughly, dried in the sun, removed from fibrous root, and cut into slices. Traditionally, Rhizoma Curcumae longae can be used in treatment of pains and tumour induced by Qi and blood stasis.

Major chemical components in Rhizoma Curcumae longae are volatile oil (6%) composed of a number of monoterpenes and sesquiterpenes, including zingiberene, curcumene, α- and β-turmerone and others. The colouring principles (5%) are curcuminoids, 50–60% of which are a mixture of curcumin, monodesmethoxycurcumin and bisdesmethoxycurcumin (WHO Monographs on Selected Medicinal Plants). Recent pharmacological studies show that Rhizoma Curcumae longae has various kinds of action, including anti-inflammation, antimicrobial, anti-oxidation, cholagogue, anti-hyperlipidemics and cardiovascular action.

There has been a long history for studies focusing on anti-tumor effect of Rhizoma Curcumae longae since Kuttan and his colleagues firstly reported its anti-cancer potential in 1985 (Kuttan et al., 1985). Recent study reveals the anti-tumor activity of radix curcumae extract on human cervical cancer cells in vitro and in vivo by inducing, G1 cycle arrest, apoptosis and inhibiting proliferation. Molecular events invovled include retinoblastoma protein dephosphorylation, reduced amounts of cyclins D1 and D3, and cyclin-dependent kinase 4 and 6 proteins, caspase activation and PARP cleavage; mitochondrial membrane potential loss by Mcl-1 and Bcl-xL reduction and reduced PTEN, AKT, and STAT3 phosphorylation and downregulation of NFkappaB signaling (Lim et al., 2010). The anti-carcinogenic effect of Curcuma longa was further demonstrated in MNNG-induced tumorogenesis model, where the herbal extract reduces the expressions of VEGF, COX-2 and PCNA and inhibits gastric cancer growth (Lu, et al., 2010). Moreover, recent study exhibits the immunostimulatory activities of polysaccharide extract of Curcuma longa, indicating its potential as an adjuvant supplement for cancer patients, whose immune activities were suppressed during chemotherapies (Yue et al., 2010). As the major active compound discovered in Curcuma longa, curcumin is also under extensive study on its anti-tumor activity and underlying mechanism. Sahu et al reported that curcumin is able to induce G2/M cell cycle arrest in human pancreatic cancer cells. Phosphorylation of Chk1 at
Ser-345, Cdc25C at Ser-216 and a subtle increase in ATM phosphorylation at Ser-1981 are observed and silencing the Chk1/ATM pathway attenuated curcumin’s effect on cancer cell cycle (Sahu et al., 2009). Another study also exhibits curcumin’s action on G1/S phase of cell cycle in human prostate cancer cells, which is correlated with curcumin-induced expression of cyclin-dependent kinase (CDK) inhibitors p16(INK4a), p21(WAF1/CIP1) and p27(KIP1), and the suppression of cyclin E and cyclin D1, and hyperphosphorylation of retinoblastoma (Rb) protein (Srivastava, et al., 2007). Curcumin could also depolymerizes mitotic microtubules, perturbs microtubule-kinetochores attachment and disturbs the mitotic spindle structure. Perturbed localization of the kinesin protein Eg5 and subsequent monopolar spindle formation is induced by curcumin. Further, curcumin increases the accumulation of Mad2 and BubR1 at the kinetochores and activate the mitotic checkpoint to induce apoptosis (Banerjee et al., 2010). Curcumin is able to induce apoptosis by some other pathways. Chen et al shows that curcumin could activate Bax expression and suppress Bcl-2 to change the Bax/Bcl-2 ratio, and decrease the mitochondrial membrane potential to led to Cytochrome C release, caspase-9 and -3 activation and PARP cleavage. Blockade of caspase pathway attenuates curcumin’s effect on apoptosis induction in human A549 lung adenocarcinoma cells (Chen et al., 2010). Curcumin also induces apoptosis through activate FAS and FADD, and triggers caspase-3 independent apoptotic cell death (Lu et al., 2009). Moreover, Curcumin was reported to inhibit tumor growth through some other different pathways. Choi et al states that curcumin interrupts the interaction between the androgen receptor and Wnt/beta-catenin signaling pathway in LNCaP prostate cancer cells by suppressing the beta-catenin expression, and therefore inhibits the prostate tumor growth (Choi et al., 2010). Another study reveals that curcumin’s inhibitory effect of tumor growth is correlated with Sp transcription factor-regulated decreased expression of NF-kappaB and its downstream genes such as cyclin D1, survivin, and vascular endothelial growth factor that contribute to the cancer phenotype (Jutorru et al., 2010). Ning et al reports that curcumin is able to down-regulate the Notch1 Intracellular Domain and inhibits the Notch1 signaling, which is correlated with the induction of cleaved poly ADP-ribose polymerase (PARP), the degradation of cyclin D1 and increase in cyclin-dependent kinase p21. This notch1 inhibition contributes to curcumin’s inhibitory effect on hepatocellular carcinoma growth (Ning et al., 2010).

Oxidative stress is also involve as an important mechanism of curcumin’s anti-tumor effect. Curcumin could potentiate paraptosis in human breast cancer cells by promoting vacuolation from swelling and fusion of mitochondria and/or the endoplasmic reticulum (ER). The paratosis inhibitor AIP-1/Alix protein was downregulated by curcumin, and AIP-1/Alix overexpression attenuated curcumin-induced death in these cells (Yoon et al., 2010). Reactive oxygen species induced by curcumin in human non-small cell lung cancer cell triggers Bcl-2 protein’s degradation, and sensitzes cells to detachment-induced anoikis (Pongrakhananon et al., 2010). However, curcumin was also reported to be an anti-tumor agent in oxidation-resistant cells, and gamma- glutamyltranspeptidase inhibition play the major role in curcumin’s effect (Quiroga et al., 2010). In addition, curcumin is also reported to induce an apoptosis-independent cell death in human cancer cells (O’Sullivan-Coyne et al., 2009). Moreover, curcumin exhibits its anti-migration action on nasopharyngeal carcinoma cells through up-regulation of E-cadherin, indicating its potential as an anti-metastasis agent (Wong et al., 2010).

As a novel molecular event in cancer progress, microRNA has been demonstrated for its important role in regulating human tumorigenesis. Curcumin was also reported to target to miRNA to exert its anti-tumor activity. Zhang et al reports that curcumin down-regulates
the expression of miR-186* in and overexpression of miR-186* significantly inhibited curcumin-induced apoptosis in A549/DDP cells (Zhang et al., 2010). Curcumin could also alter miRNA expression in human pancreatic cells, up-regulating miRNA-22 and down-regulating miRNA-199a*, and up-regulation of miRNA-22 expression by curcumin in pancreatic cancer cells suppresses expression of its target genes SP1 transcription factor (SP1) and estrogen receptor 1 (ESR1), which may be correlated with curcumin’s anti-cancer activity (Sun et al., 2008).

Similar to the crude extract, curcumin exhibits immunomodulatory property in suppressing the induction of indoleamine 2,3-dioxygenase by blocking the Janus-activated kinase-protein kinase C delta-STAT1 signaling pathway, and showed its potential as an adjuvant agent in cancer chemotherapy (Jeong et al., 2009).

4.4 Radix stephaniae tetrandrae (Han Fangji in Chinese)

Radix stephaniae tetrandrae is the dried root of Stephania tetrandra S. Moore (Menispermaceae). With its Chinese name as Han Fangji, it was firstly recorded in Shennong Bencao Jing. Commonly called as Stephania root or Tetrandra root, the Radix stephaniae tetrandrae is considered to be bitter, cold and pungent, and belongs to the meridians of Urinary bladder, kidney and spleen. Han Fangji is distributed in Shanxi, Yunnan and Guangxi Province of China. It is used to dispel wind and dampness, and to relieve edema and pain in Chinese Medicine clinical practice.

The phytochemical study on Radix stephaniae tetrandrae exhibits that it contains several kinds of alkaloids, including Tetrandrine, Fangchinoline, Cyclanoline and Trilobine. Recent pharmacological studies show that Radix stephaniae tetrandrae and its compounds has anti-inflammatory (Shen et al., 2001), antihypertensive, anti-arrhythmic (Yu et al., 2004), and cardiovascular action (Wong et al., 2000).

The whole extract or chemical fraction of Radix stephaniae tetrandrae was rarely reported for its anti-tumor activity either in vitro or in vivo. The reason behind may be that one of other plants, Aristolochia fangchi, was used as a substitution of Stephania tetrandra due to their similar name in Chinese (Guang Fangji for Aristolochia fangchi and Han Fangji for Stephania tetrandra). Several years ago, several studies reported that urothelial carcinoma is associated with the use of Aristolochia fangchi, which contains nephrotoxic and carcinogenic aristolochic acids, to replace Stephania tetrandra (Nortier et al., 2000). However, a recent report that a Stephania tetrandra-containing Chinese Herb Formula, SENL, could reduce the expression of multi-drug resistance-associated protein and increase the intracellular accumulation of chemotherapeutic agent, Adriamycin, in human lung cancer cell line SW1573/2R120 (Xu et al., 2010), indicating Stephania tetrandra could be used as a complementary agent in chemotherapy to enhancing cancer cell sensitivity to chemotherapeutic agents. In contrast, as the major compound isolated from Stephania tetrandra, tetrandrine is extensively reported for its anti-tumor activity in various human cancers. Tetrandrine induces human cancer cell cycle arrest at G1 by first, inhibiting cyclin-dependent kinase 2 (CDK2)/cyclin E and CDK4 and second, inducing the proteolysis of CDK4, CDK6, cyclin D1, and E2F1 in HT-29 cells (Meng et al., 2004). Consistent observation of G1 arrest action of tetrandrine could be also found in another study and may be attributable to tetrandrine’s inhibitory effect on AKT pathway. Inhibition of Akt could subsequently activate GSK3β and upregulate p27 (Chen et al., 2008). Tetrandrine was also reported to be capable of inducing cell apoptosis in various kinds of human cancers, including lung carcinoma (Lee, et al., 2002), leukemia (Jang et al., 2004), hepatoma (Ng et al., 2000), and others.


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This book is addressed to scientists and professionals working in the wide area of biomedical engineering, from biochemistry and pharmacy to medicine and clinical engineering. The panorama of problems presented in this volume may be of special interest for young scientists, looking for innovative technologies and new trends in biomedical engineering.

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