Molecular and Cellular Mechanism Studies on Anticancer Effects of Chinese Medicine

Yigang Feng[1], Ning Wang[2], Fan Cheung[2], Meifen Zhu[2],
Hongyun Li[1] and Yibin Feng[2]*
*[1]Guanhau School of Stomatology, Hospital of Stomatology, Sun Yat-sen University,
Guangzhou,*
*[2]School of Chinese Medicine, The University of Hong Kong, 10 Sassoon Road, Pokfulam,
Hong Kong,*
PR China

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 enviroments (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 celluar mechanism studies on anticancer action of Chinese medicines by trend prediction from top journals of Chinese medicine, ethnomedicine, alternative and complemental medicine. 12 representative Chinese medicines were selected in this chapter (Rhizoma coptidis, arsenic, Rhizoma Curcuma longae, Radis stephaniae tetrandrae, Radix tripterygii 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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* Corresponding author: E-mail: yfeng@hku.hk

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 enviroments (protection of endangerous species from animal and plants) have also become emerging issues. On the other hand, research mainly focused on sigle Chinese medicines in the past decades, we should do more studies on composite fomulae (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 ect. 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 Pharmacopeia (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), cholangecarsinoma 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-1β (IL-1β) and Tumor necrosis factor-α (TNF-α) productions via inhibiting the phosphorylation and degradation of inhibitor of kappa B-α (IκB-α) (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

al., 2010). Our results suggests that CR and berberine are promise alternative therapy in treatment of cancers. Computer–aided molecular design and prediction of cell response to CR, berberine and analogs, and genomics and proteomics, microRNA approaches to study antineoplastic effects of berberine and Huanglian are expected in the future. The relatively low toxicities at therapeutic level for both Huanglian and berberine also show additional benefit 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 Nedica, 973 A.D.). Arsenic has various forms. The most important compounds of arsenic are arsenic trioxide, As_2O_3, ("white arsenic"), the yellow sulfide orpiment (As_2S_3) and red realgar (As_2S_2). 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 (As2O3) [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 As_2O_3 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 As_2O_3 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 As_2O_3 [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, anti-microbial, anti-oxidation, cholagogue, antihyperlipidemics and cardiovasucular action.

There has been a long history for studies focusing on anti-tumor effect of Rhizoma Curcumae longae since Kuttan and his collegues 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 domonstrated 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, whcih 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, perturbes microtubule-kinetochore attachment and disturbes the mitotic spindle structure. Pertubed 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 motochondrial 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 grwoth (Choi et al., 2010). Another study reveals that curcumin's inhibitory effect of tumor growth is correlated with Sp transcrption 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 inhibtion contributes to curcumin's inhibitory effect on hepatocellular carcinoma growth (Ning et al., 2010).

Oxdiative 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 degrdation, and sensitizes 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 tumoriogenesis. 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 Cdelta-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 an 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 mutildrug 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.,

2006), nasopharyngeal carcinoma (Sun et al., 2006) and colon cancer (Chen et al., 2008). Jang et al. stated that tetradrine could induce early oxidative stress and produce ROS in human U937 cells and this result in activation of JNK pathway. However, the activation of JNK is not responsible for tetrandrine-induced apoptosis but caspase-dependent generation of a catalytically active fragment of PKC-delta may play a role (Jang et al., 2004). Sun et al. reported that tetradrine is able to induced apoptosis in human nasopharyngeal carcinoma cells CNE and this effect results from the increased expression of pro-apoptotic Bax mRNA transcript and decreased expression of anti-apoptotic factor Bcl-2 mRNA transcript (Sun et al., 2006). Wu et al. showed that apoptosis could be induced by tetrandrine in colon cancers and the increased expression of Erk1/2 and p38 MAPK are observed. However, only p38 MAPK is responsible for tetrandrine-induced apoptosis in CT-26 cells (Wu et al., 2010). However, Cho et al. stated that tetrandrine selectively inhibits the proliferation of lung cancer cells by blocking Akt activation and increases apoptosis by inhibiting ERK in human lung carcinoma cellA549 (Cho et al., 2009). These studies indicate the multiple targets of tetrandrine in treating human cancers. In addition, tetrandrine was reported to inhibit gliomas angiogenesis by suppressing the VEGF expression in gliomas cells (Chen et al., 2004) and suppress pulmonary metastases of colorectal adenocarcinoma (Chang et al., 2004), where F-actin and microtubule remodeling may be involved (Lee et al., 2002). Moreover, tetrandrine was extensively reported for its capacity in reducing multidrug resistance (MDR) by inhibiting MDR-related protein P-gp at either expression or enzymatic level and increasing the efficacy of chemotherapeutic agent (Shen et al., 2010). However, it is contradictory to observe no significant difference between the doxorubicin pharmacokinetic parameters obtained in mice received doxorubicin only and doxorubicin combined with tetrandrine (Dai et al., 2007). Further study may be required to assure the exact action and mechanism of tetrandrine in helping chemotherapeutic agents to overcome the MDR in human cancer. Another major compound in Radix stephaniae tetrandrae, fangchinoline, also exhibits reversal effect on the MDR of cancer cells in response to chemotherapeutic agents paclitaxel and vinblastin via modulation of P-gp (Chio et al., 1998; Wang et al., 2005), however, very few studies were focusing on its anti-tumor mechanism. A recent investigation reports that fangchinoline could induce G1/S phase cycle arrest via inhibiting Cyclin D1 and overexpressing p27 in human prostate cancer cell PC3. In addition, fangchinline is able to potentiate cancer cell apoptosis by inducing pro-apoptotic Bax and down-regulating anti-apoptotic Bcl-2. Inhibition of prostate cancer in xenograft model by fangchinline was also observed (Wang et al., 2010). Our on-going study shows that fangchinoline could not induce apoptosis in human hepatocellular carcinoma cells though the potent cell death could be observed when exposed to low dose of fangchinoline, indicating an althernative cell death model may be involved in fangchinoline's effect. We found that autophagic cell death may be the substitute and activation of AMPK signaling may play a role.

There is no report on the adverse reaction of Radix stephaniae tetrandrae, but overdose of Radix stephaniae tetrandrae (4.5-9 grams in decoction is appropriate) may induce vomiting, tremor, ataxia, convulsions, quadriplegia, hypertonicity, and respiratory failure.

4.5 Radix tripterygii wilfordii (Lei Gongteng in Chinese)

Radix Tripteryii Wilfordii is the dried root of Triptrygium Wifordii Hook F. It is a native plant that grows widely in China, distributed in Zhejiang, Anhui, Jiangxi, Hu'nan, Guangdong, Guangxi, Fujian, Taiwan and Yunnan province. It is used to dispel wind and

dampness, and to relieve arthritis and pain in Chinese Medicine clinical practice. Anticancer application is a new use for Radix tripterygii wilfordii.

The phytochemical study on Radix tripterygii wilfordii indicates that it contains various kinds of alkaloids, including wilfordine, wilforine, wilforidine, wilforgine, wilfortrine, wilforzine, wilformine, wilfornine, euonine, celacinnine, celafurine, celabenzine, neowilforine, regilidine and terpenoids, including triptolide T13, tripdiolide, tripterolide, triptonide, triptolidenol T9, hypolide, triptonoterpenol, triptophenolide methylether, neotriptophenolide, isotriptophenolide, isoneotriptophenolide, triptonoterpene, triptonoterpene methylether, tripdioltonide, tripdiolide T8, triptriolide T11, triptolide T10, wilforlide AT1, triptotriterpenoidal lactone A, wilforlide B, triptotriterpenic acid AT3, triptotriterpenic acid BT2, triptoterpenic acid CT28, selaspermic acid, wilfornide, triptofordin A,B,C-1,C-2, D (Xian et al., 1997).

Tripteryii Wilfordii was traditionally used as an important medicine for thousand of years in Chinese Medicine to treat the syndrome associated with immune- inflammatory diseases (Jia, 1985). However, it has been shown to have multiple uses in Chinese medicine of not only immune-inflammatory diseases, but also cancers, neurodegenerative diseases and fertility regulation (Brinker et al., 2007).

Triptolide is the predominant bioacitive compound which is isolated from Radix Tripterygii wilfordii (Zhou et al., 2010). A lot of studies show that triptolide has the anti-cancer effect by inducing cell apoptosis in several kinds of cancers, including leukemia (Lou et al., 2004), colorectal cancer (Min, 2010; Xu et al., 2010), Cholangiocarcinoma (Clawon et al., 2010; Lou et al., 2004), pancreatic cancer (Chen et al., 2010; Chang et al., 2010) and breast cancer (Liu et al., 2009). The latest research showed that triptolide has the anti-cancer effect via inducing cell death in pancreatic cancer cells via autophagy and apoptosis (Mujumdar et al., 2010). Mujumdar et al. reported that triptolide could induce autophagy by some specific genes, atg5 or beclin 1. Some studies indicate that triptolide inactivated the Protein kinase B (Akt)/ mammalian target of Rapamycin/ p70S6K pathway and up-regulated the expression of Extracelluar Signal-Related kinase (ERK) 1/2 pathway to promote apoptosis in pancreatic cancer cell lines (Mujumdar et al., 2010). Wang et al. showed that triptolide has the anti-cancer effect on acute myeloid leukemia by causing down-regulation of C-KIT and inhibiting the JAK-STAT signaling, which is the same as the situation in colon cancer (Wang et al., 2009). Moreover, the expression of p65 was decreased by triptolide, which inhibits the DNA-binding activity of NF-kappaB. Triptolide also has been shown to have the ability of decreasing cell viability in all cell lines at 48h via activating caspase-3 (Clawon et al., 2010). In endometrial and ovarian cancer cells, triptolide has been reported to have the anti-growth activity via targeting some specific genes, such as LRAP, CDH4, SFRP1 and so on (Li et al., 2010). Besides, some studies indicate that triptolide could act as the inhibitor of RNA polymerase I and II-dependent transcription promoting some short-lived mRNA, for example cell cycle regulator CDC25A (Vispé et al., 2009).

Celastrol is another main component isolated from radix tripterygii wilfordii, which has been reported to have the anti-cancer effect in cancer cell lines including leukemia (Lu et al., 2010), glioma (Zhou et al., 2009) and so on. Lu et al. reported that celastrol could decrease the protein levels of Bcr-Abi and inhibit the growth in chronic myelogenous leukemia (Lu et al., 2010). Zhou et al. showed that celastrol has the anti-angiogenic effect in human glioma via in vitro and in vivo study (Zhou et al., 2009). The other studies denoted that celastrol could suppress the tumor growth mediated by angiogenesis by inhibiting AKT pathway (Pang et al., 2010).

The side effects of tripterygii wilfordii include gastrointestinal upset, infertility and suppression of lymphocyte proliferation (Chou et al., 1995).

4.6 Radix scutellariae (Huangqin in Chinese)

Radix scutellariae with the Chinese name of Huangqin, is the root of Scutellaria baicalensis Georgi (Labiatae). It is native to Jilin, Liaoning, Shanxi, Henan, Inner Mongolia and Hebei Province of China. Radix scutellariae can be obtained from wild or cultivated species. Roots of the herbs are dried for medical use. Fruits are also collected and used as herbal drugs. It can be used in treatment of symptomes induced by damp-heat or heat-toxicity which can be convinced to be diseases related to infection or inflammation in Chinese medicine clinical practice.

Radix scutellariae includes a series of flavones and their derivatives, such as baicalein, baicalin, chrysin, 5,6-dihydroxy-7-O-glucoside-flavone, 5,7,2'-trihydroxy-flavone, 5,7,2', 3'-tetraflavone, 5,7,2',6'- tetraflavone, 5,7,2'-trihydroxy-8-methoxyflavone, oroxylin-A-glucoronide, oroxylin-A, 5,7,2'-trihydroxy- 6-methoxyflavone, nor-wogonin, Wogonin, Wogonoside, 5,8,2'-trihydroxy-7-methoxyflavone, Wogonoside, Scutevulin, etc. Other chemicals in Huangqin include proline, acetophenone, palmitic acid, etc. According to China Pharmacopeia (Edition 2005), baicalin is used as quality criteria for raw Radix scutellariae, and the content of bacalin should not be lower than 9.0% for the raw material.

It was reported that the stem and leaves of Radix scutellariae reveals potent anti-bacterial effect in vitro study (Zhao et al., 2007). Some studies indicated that the ethyl acetate extracting fraction showed the best anti-bacterial effect among fractions isolated from Radix scutellaria (Ren et al., 2005). Total flavones from stem and leaf of Radix scutellaria showed preventive effect against experimental hyperlipidemia (Yi et al., 2005).

Modern studies denoted that Radix scutellaria has anti-cancer effect in various kinds of cancer cell lines including breast cancer cell (Zhou et al., 2009; Wang et al., 2010), lung cancer (Gao et al., 2010), leukemia (Kumagai et al., 2007), prostate cancer (Miocinovic et al., 2005) and so on.

It was reported that anti-proliferative and apoptotic activity against acute lymphocytic leukemia, lymphoma and myeloma cell lines (Kumagai et al., 2007). The predominant of the anti-cancer effect of baicalin has been shown to induce apoptosis (Lian et al., 2003). The investigation of baicalin showed that it could induce prostate cancer cell line DU 145 apoptosis in vitro via inhibiting Bcl-2 and Bax while up-regulating Fas (Gu et al., 2005). Wang et al. reported that baicalin induced breast cancer cells apoptosis by increasing the expression of p53 and Bax (Wang et al., 2008). Besides, some studies indicated that the cancer cell death and proliferation retardation may be induced by the inhibition of CDC2 kinase and survivin associated with opposite role of p38 mitogen-activated protein kinase and AKT (Chao et al., 2007). Moerover, Sun et al. showed that baicalin played the role of suppressing MDA-MB-435 human breast cancer cells invasion by decreasing matrix metalloproteinase-2/9 (Sun et al., 2009).

Another active compound, wogonin, has also been reported to induce apoptosis in cancer cell lines (Li, 2010). Lee et al. showed that wogonin could involve in the regulation of apoptosis in human cancer cells which may associate with p53, PUMA, and Bax (Lee et al., 2008). Zhao et al. also reported that wogonin exert anti-cancer effect via decreasing the expression of NF-KappaB which induced apoptosis (Zhao et al., 2010). Besides, wogonin has been shown to delay cancer cell growth through inhibiting Akt, GSK-3 and NF-KappaB signaling (Parajuli et al., 2010).

Clinical adverse reactions include: gastric discomfort and diarrhea; fever reaction after i.v. injection of baicalin at dose of 150 mg (Bi, 1998; Nemoto et al., 2002)

4.7 Herba artemisiae annuae (Qinghao in Chinese)

Qinghao is the aerial part of Artemisia annua L. (Compositae). It is native to Hebei, Shandong, Jiangsu, Hubei and Fujian Province of China. Qinghao can be obtained from wild or cultivated species. It is used for fever and antimalaria in Chinese medicine clinical practice.

Artemisinin, artemisinin I, artemisinin II, artemisinin III, artemisinin IV, artemisinin V arteannuic acid, aremisilactone and artenimol and their derivations are the main composition of raw material of Qinghao. The major pharmacological action of Qinghao includes antimalaria, antiviral, treatment of schistosomiasis and anticancer activity (Feng et al., 2010).

A systematic screening on the active components in Herba artemisiae annuae with cytotoxicity on serveral human tumor cell lines was investigated in 1994, which then started the cellular and molecular mechanism study of the anti-tumor activity of compounds from Herba artemisiae annuae. Artemisinin and quercetagetin 6,7,3',4'-tetramethyl ether showed significant cy-totoxicity against P-388, A-549, HT-29, MCF-7, and KB tumor cells in this study (Zheng, 1994). As the major component in Herba artemisiae annuae, artemisinin and its derivatives were extensively reported for their anti-tumor action and underlying mechanism. The general mechanism of the anti-tumor activity of artemisinin and its derivatives may be that artemisinin-like chemical could carry iron, which is required for the proliferation of cancer cells, and form free radicals to kill the cancer cell (Lai et al., 2005). However, there are some other particular mechanisms invovled. Artemisinin is able to induce G1 arrest of the cell cycle in human hepatoma cells via regulating cyclin D1, CDK2, CDK4 and serveral other CDK inhibitos (Hou, et al., 2008). Mechanism study shows that artemisinin could disrupt the interaction of transcription factor Sp1 and CDK4 promoter and therefore suppress the expression of CDK4 (Willoughby, et al., 2009). Artemisinin is able to induce apoptosis with a caspase-3 dependent manner in cancer cells (Nam et al., 2007), and could selectively decrease functional levels of estrogen receptor-alpha to suppress the proliferation of human breast cancer cells (Sundar et al., 2008). In addition, Artemisinin could reduce cell migration in human melonoma by suppressing alpha V beta 3 integrin and reducing metalloproteinase 2 production (Buommino, et al., 2009).

Another major compound is dihydroartemisnin. A study reported that dihydroartemisinin is able to induce G1 cell cycle arrest in human pancrate carcinoma cells though regulating cyclin E, cdk2, cdk4 and p27(Kip1) (Chen et al., 2010). Dihydroartemisinin induces apoptosis through potentiating the mitochondrial transmembrane permeability, releasing cytochrome c and activating of caspases (Lu, et al., 2009). The induction of apoptosis by dihydroartemisinin is Bak- or NOXA-dependent (Handrick et al., 2010). Another study reports that the anti-cancer activity of dihydroartemisinin is associated with induction of iron-dependent endoplasmic reticulum stress in colorectal carcinoma HCT116 cells (Lu, et al., 2010). In human prostate carcinoma cells, dihydroartemisinin was observed to induce tumor cell death via extrinsic and intrinsic pathway. Transcriptional activation of the death receptor 5 (DR5) and suppression of PI3-K/Akt and ERK cell survival pathways may play a role (He et al., 2010). Studies also reveal that dihydroartemisnin exhibits anti-migration effect on human fibrosarcoma cell HT-1080 through inhibition of PKCalpha/Raf/MAPKs and NF-kappaB/AP-1-dependent mechanisms (Hwang, et al., 2010). In addition,

dihydroartemisinin improves the efficiency of chemotherapeutics in lung carcinomas in vivo, where dihydroartemisinin could help inhibit tumor growth through inducing apoptosis and suppress metastasis via down-regulating the expression of VEGF receptor KDR/flk-1 (Zhou, et al., 2010). To further expolre the active compounds in Herba artemisiae annuae, a study was carried out to compare the anti-tumor effect of compounds in Herba artemisiae annuae on chemoresistant cancer cells, and found artesunate being the most active (Michaelis et al., 2010). Artesunate was reported to induce DNA damage (Li, et al., 2008) and apoptosis (Michaelis et al., 2010) in cancer cells. Recently, an interesting investigation reported a caspase-independent mechanism of cell death induced by artesunate, an oncosis-like cell death in pancrate cancer cells. This kind of cell death is dependent on the loss of mitochondrial membrane potential and the presence of reactive oxygen species (ROS) (Du et al., 2010). Moreover, artesunate exhibits anti-angiogenic effect in human ovarian cancer through inhibiting the VEGF receptor KDR/flk-1 expression (Chen et al., 2004). Finally, recent study shows that the old member of the artemisinin derivates artemisone also exhibits significant anti-tumor effect (Gravett et al., 2010). These extensive studies reveal the potential of compounds from Herba artemisiae annuae for anti-cancer therapy in clinical practice.

4.8 Radix Ginseng (Renshen in Chinese)

Radix Ginseng, the dried root of Panax ginseng C.A. Meyer (Araliaceae), has been widely used as a tonic agent in traditional Chinese medicine for improvement in physical and mental capacities. The earliest written account of Radix Ginseng is from "Shen Nong Ben Cao Jing" (Shen Nong's Materia Medica, circa A.D. 100). Its species include Radix ginseng cruda, Radix ginseng rubra and Radix ginseng silvestris, and is mainly produced in Jilin, Liaoning, Heilongjiang Provinces of China and Korea. Wild ginseng is called "Shanshen", whereas the cultivated ones are known as "Yuanshen" (Garden Ginseng), of which, the sun-dried or bake-dried are called "Shengshaishen" (Sun-dried Ginseng). The fresh ginseng, which is made by steaming and then drying under the sun or heat, is called "Red Ginseng" (Radix ginseng rubra). The sun-dried and freezing-dried wild ginseng is named "Sun-dried Wild Ginseng" [Pharmacopoeia of the People's Republic of China, 2000].

Numerous constituents of radix ginseng such as ginsenosides (ginseng saponins), polysaccharides, peptides, polyacetylenic alcohols, aminoglycosides, and ginseng oils have been found and characterized. Among these, ginsenosides are believed to be the main active constituents in the pharmacological actions of ginseng. Ginsenosides are triterpenoid glycosides of dammarane and oleanane structures and so far more than 30 ginsenosides have been isolated from radix ginseng. According to the chemical structure characteristics, ginsenosides can be divided into three groups: panaxadiol, panaxatriol and oleanolic acid [Chang et al., 1992].

There is an increasing interest in radix ginseng regarding the human cancers. It is believed that the life-prolonging effect of radix ginseng may be because of the protective effect against various cancers such as prostate cancer, ovarian cancer and lung adenocarcinoma [Kim et al., 2004; Liu et al., 2000; Nakata et al., 1989]. Ginsenosides are the major antitumor constituents in radix ginseng. In a recent study in Korea, ginsenoside Rp1 was examined the anti-metastatic activities using in vitro assays and in vivo metastasis models [Tae et al., 2008]. This study suggested that ginsenoside Rp1 might act as an anti-cancer agent by strongly inhibiting cell viability and metastatic processes, presumably by inhibiting the adhesion of tumor cells and vessel formation. Another study in Hong Kong indicated that

ginsenosides might act in a similar way as steroid hormones attributes to the effect in anti-cancer. The study found that ginsenosides can act as functional ligands to activate different steroid hormone receptors [Yue et al., 2007]. The results of the study showed that the anti-tumour effects of ginsenosides included its ability to induce cell death (such as apoptosis and necrosis), and having effects of anti-proliferation, anti-invasion and metastasis, and anti-angiogenesis. Moreover, ginseng has been found to be a therapeutic agent for renal cell carcinoma (RCC) [Jeongwon et al., 1998], a disease which many patients having been diagnosed to be in metastatic status at initial diagnosis [Lam et al., 2005]. It was suggested that lipid soluble components of ginseng inhibit the growth of RCC cell lines by blocking cell cycle progression at G1 to S phase transition. Furthermore, ginseng has been established as non-organ specific cancer prevention [Yun, 2001]. There was a dose-response relationship that was showed between the decreased risk of cancer with increased ginseng intake.

A "ginseng-abuse syndrome" was reported in 14 of 133 long-term ginseng users [Siegel, 1979]. These patients experienced hypertension, nervousness, sleep-lessness, skin eruptions and diarrhoea; some subjects also became euphoric and agitated. Doses of 15 g were associated with depersonalization and confusion, while depression was reported after more than 15 g per day. Moreover, estrogenic-like side effect of ginseng had been published [Punnone et al., 1978]. Furthermore, it was reported that ginseng might inhibit the effects of warfarin [Janetzky, 1997] and interact with the monoamine oxidize inhibitor phenelzine [Jones et al., 1987].

4.9 Radix notoginseng (Sanqi/Tienchi in Chinese)

Radix notoginseng is the dried root of Panax notogiseng (Burk.) F. H. Chen (Araliaceae). It was first recorded in "Compendium of Materia Medica" ("Bencao Gangmu" in Chinese) by Li Shizhen (1518–1593 A.D.). Radix notoginseng has a long history of use as a traditional herbal medicine due to its blood circulation promotion, blood stasis removal and pain alleviation effects, and has been widely utilized for the prevention and treatment of microcirculatory disturbance in Oriental countries [Lee et al., 2009]. The herb is slightly bitter in favor, non-toxic and is mainly cultivated in Wenshan region, Yunnan province in China.

Similar to P. ginseng C. A. Meyer and P. quinquefolius L., P. notoginseng contains saponins as its main bioactive constituents, commonly referred to as ginsenosides, notoginsenosides and gypenosides. Other types of constituents extracted from Radix Notoginseng such as essential oils, amino acids, polysaccharides, dencichine and flavonoids are also pharmacologically active and have a function on some diseases [Modern Chinese Materia Medica, 2007].

Recently, several studies have demonstrated the inhibitory effects of Radix Notoginseng extract against a variety of human cancers, such as skin tumours, cervical cancer, prostate cancer, gastric cancer, colorectal cancer, sarcoma and breast cancer [Ng, 2006]. Laboratory studies on colorectal cancer suggested that Radix Notoginseng could be used alone or as adjuncts to existing chemotherapy to improve the outcomes of the chemotherapeutic treatment and reduce the adverse effects of chemotherapy [Wang et al., 2007; Wang et al., 2009; Sadeghi and Yazdanparast, 2005; Zhang et al., 2007]. These Studies found that the anti-proliferative activity of Radix Notoginseng extract was most probably because of cell cycle arrest, which the cancer cells were arrested in S phase and G2/M phase, and the induction of cancer cell apoptosis. Wang's group also suggested that the anti-proliferative effects of Radix Notoginseng were in a concentration-dependent manner. Nowadays, the induction of

cancer cell apoptosis, which is a programmed cell death, is an important therapeutic mechanism in anti-cancer drug. The mechanism of the induction of apoptosis in human cancer cells, such as lung carcinoma cells, cervical cancer cells and gastric cancer cells, by Panax Notoginseng extracts (PNE) was investigated in the recent studies. The studies showed that PNE treatment significantly inhibited the cell viability and induced cancer cell death in a dose-dependent manner. Furthermore, the results of these studies indicated that the major regulators of PNE-induced apoptosis in human carcinoma cells are the Bcl-2 family and caspase-3, which are associated with mitochondrial dysfunction and dephosphorylation of the Akt signaling pathway [Park et al., 2009; Yang et al., 2006; Li et al., 2008]. Except the inhibition of cancer cell proliferation and the induction of apoptosis, the regulation of gap junctional intercellular communication (GJIC) was believed to play an important role in cancer prevention [Ruch, 1994]. Recently, a study on human hepatocarcinoma cells suggested that Radix Notoginseng saponins could up-regulate or recover GJIC function which was in a concentration-dependent manner [Shang et al., 2006].

Minor allergic effects of Radix Notoginseng were reported in some studies [Yang et al., 2002]. The allergic reactions were likely due to the low quality of Radix Notoginseng use.

4.10 Radix Astragali (Huangqi in Chinese)

Radix Astragali (RA) is derived from the dried roots of Astragalus membranaceus (Fisch.) (Leguminosae). Bunge and Astragalus membranaceus (Fisch.) Bunge var. mongholicus (Bunge) Hsiao are two commonly used species. RA is mostly prepared from cultivated ones, as wild ones are increasingly scarce, mainly produced in the northern part (Shanxi, Neimenggu, and Hebei) and the northeastern part (Heilongjiang) of China. Recent studies indicated that Shanxi of China produced the best quality of Radix Astragali [Ma et al., 2000].The earliest scientific description of RA was in Shen Nong Ben Cao Jing, a materia medica book edited in the 1st century. It has been traditionally used as a qi-tonifying drug or an adaptogenic herb in Chinese medicine for thousands of years. RA is prescribed as an immunostimulant, hepatoprotective, anti-perspirant, a diuretic or a tonic, and is used for treatment of many diseases in Chinese medicine clinical practice [Sinclair, 1998].

Regarding the chemical constituents of RA, more than 100 compounds have been isolated and identified up to now, and the most often associated with the biological activity of RA are isoflavonoids, triterpene saponins, polysaccharides, amino acids, and various trace elements [Chen et al., 2008; Gui et al., 2006; Lin et al., 2000]. Among these, astragaloside IV (one of the two main saponins), calycosin and formononetin (two of the three major active isoflavonoids) are normally being used as makers for RA's quality control [Song et al., 2004]. Sinclair's study found that RA has a wide range of immunopotentiating effects, and has been used extensively as an adjuvant in cancer therapy and as a phytochemical immune modulator. A study on the effects of RA extract reported that RA lowered the incidence of urinary bladder carcinoma in N-butyl-N'-butanolinitrosoamine treated mice by activating the cytotoxicity of lymphocytes and increasing the production of IL-2 and IFN-γ [Kurashige et al., 1999]. Another study indicated that RA extract significantly increased the activity of IL-2, of B cell growth factor and IL-6 in vitro and of phytoemagglutinin-induced proliferation of T lymphocytes from patients with IgG subclass deficiency [Tu et al., 1995]. Renal cell carcinoma has been shown to produce factors which may impair the normal functions of the immune system, such as macrophage function suppression. A laboratory study found evidence that RA restored the chemiluminescent oxidative burst activity of murine splenic macrophages which were shown to be suppressed by renal cell carcinoma. It

was also suggested that RA might have exerted its anti-tumor effect via augmentation of phagocyte and lymphokine-activated NK cell activities in vivo [Lau et al., 1994; Yang et al., 1998]. Guanine nucleotide exchange factors (GEFs) (oncogenes), such as Vav proteins (Vav1, Vav2 and Vav3) are hyperactive in various cancers. A recent study demonstrated that Vav3.1 expression was down-regulated by astragaloside IV in a dose- and time-dependent manner which might be highly correlated with the inhibition of the cellular malignant transformation. Thus, the study suggested that astragaloside IV might elicit anti-cancer activity via down-regulating the expression of oncogenes such as Vav3.1 [Qi et al., 2010]. It was revealed that RA could induce erythroleukemia cell lines to undergo cell differentiation and cell death which the up-regulation of Apaf-1, caspase-3 and AChE activation might play a crucial role during the process of apoptosis in cancer cells [Cheng et al., 2004]. Apart from the above actions, it was also showed that Astragalus polysaccharides could counteract the side effects of chemotherapeutic drugs, such as a significant reduction in the degree of myelosuppression in cancer patients [Tin et al., 2007].

In general, RA was safe without any distinct adverse effects [Sinclair 1998; Yu et al., 2007].

4.11 Radix angelicae sinensis (Danggui in Chinese)

Radix angelica sinensis (AS) is the dried root of Angelica sinensis (Oliv.) Diels (Umbelliferae) and is indigenous to China. AS is rarely available in the wild and is currently cultivated and harvested in late autumn after three years. It is mainly cultivated in Gansu province and partly in Yunnan, Sichuan, Shanxi, Hubei and Guizhou provinces of China. AS was first documented in Shen Nong Ben Cao Jing around 100 A.D.. According to the medicinal theory of traditional Chinese medicine, AS is used to tonify blood, improve blood circulation, regulate menstruation, and lubricate the bowels to alleviate constipation. Clinically, it has been commonly applied to the treatment of gynecological disorders (such as menstrual disorders, anemia, premenstrual syndrome and menopause), cardiovascular diseases, cerebrovascular diseases, cancer and high blood pressure for a long time. It was first introduced into western countries in 1899 by Merck in the form of a liquid extract named "Eumenol" and is presently marketed the United States as a dietary supplement, with numerous related commercial products for women's care worldwide [Deng et al., 2006].

Currently, over 70 compounds have been isolated from AS and identified [Dong et al., 2007]. The main chemical constituents of AS are ferulic acid, ligustilide, angelicide, brefeldin A, butylidenephthalide, butyphthalide, succinic acid, nicotinic acid, uracil, and adenine. The constituents most often associated with the pharmacological activities of AS are ferulic acid and ligustilide (predominantly the Z-isomer), both of which are usually used as chemical markers for the quality control of AS [Liu et al., 2000; Song, 1996].

Clinical studies showed that AS had anti-cancer capabilities in various human cancers. One study showed the inhibitory effect of AS on growth and proliferation of glioblastoma multiforme (GBM). The lipid-soluble ingredients of AS were extracted with acetone (AS-AC) or chlorophenol (AS-CH) and their antiproliferative and proapoptotic effects were studied in cultured GBM 8401 cells and in tumors in nude mice. Both extracts significantly inhibited the proliferative activity of GBM 8401 cultured cells by decreasing the expression of VEGF and the proapoptotic protein, cathepsin B, as this compound induced cancer cell cycle arrest at the G0-G1 phase which led to apoptosis. Both fractions significantly inhibited microvessel formation in the tumors of nude mice [Lee et al., 2006]. Growth suppression of malignant brain tumor cells by AS-CH resulted from cell cycle arrest and apoptosis. AS-CH up-

regulated expression of cdk inhibitors, including p21, to decrease phosphorylation of Rb proteins which resulted in cell cycle arrest at the G0-G1 phase in human DBTRG-05MG and rat RG2 cells. The apoptosis-associated proteins were dramatically increased and activated in DBTRG-05MG cells and RG2 cells by AS-AC but without p53 protein expression in RG2 cells. In vitro results showed that AS-AC triggered both p53-dependent and p53-independent pathways of apoptosis [Tsai et al., 2005, 2006]. AS-AC and AS-CH also significantly inhibited microvessel formation in vivo. All these findings suggested that AS possessed anti-tumor effects and might be useful in the treatment of high-grade astrocytomas. It has been found that neodiligustilide, Z-ligustilide, 11(S), 16(R)-dihydroxy-octadeca-9Z, 17-dien-12, 14-diyn-1-yl acetate and 3(R),8(S)-falcarindiol possess cytotoxic properties (Chen et al., 2007) .

N-Butylidenephthalide (BP), isolated from the chloroform extract of AS, was examined for its antitumor effects on hepatocellular carcinoma cells and might be a potential clinical use for improving the prognosis of hepatocellular carcinoma cells by inducing apoptosis in carcinoma cells in vitro and in vivo [Chen et al., 2008]. Invasion and metastasis are essential characteristics of malignant tumors. An experimental study suggested that total polysaccharide of AS (ASP) possessed anti-tumor effects on experimental tumor models in vivo and inhibitory effects on invasion and metastasis of hepatocellular carcinoma cells in vitro [Shang et al., 2003]. AP promoted the release of NO, TNF-α, and ROS and improved the activity of iNOS and lysozyme in macrophages. However, ASP had no direct cytotoxicity to tumor cells, but the culture medium of macrophages, pretreated with ASP, killed L929 tumor cells [Yang et al., 2004]. These results indicate that the extract may directly inhibit the invasion and metastasis of cancer cells, and indirectly stimulate immunological activity against cancer cell growth. Cell- mediated immune defense plays a key role in anti-tumor activity and is mediated specifically by T cells and non-specifically by macrophages and natural killer (NK) cells [Shan et al., 2002; Wang et al., 2004]. A study found that ASP had immunomodulatory activity by regulating expression of Th1 and Th2 related cytokines. The time–effect relation of cytokines response also suggested that macrophages and natural killer cells involved in nonspecific immunity were primarily activated, and helper T cell were secondarily affected by ASP [Yang et al., 2006].

AS contains several coumarin derivatives and should be used with caution in women on anticoagulants because of the increased risk of bleeding. AS also contains a carcinogenic essential oil, and some recommend that "all unnecessary exposure to dong quai should be avoided" [Israel et al., 1997]. The irritant agents in AS are believed to be the essential oils and Ligustilide is the most irritant within the essential oils of AS. An excess amount of ligustilide results in nausea, xeransis, and anesthesia of the oral cavity and tongue [Xie, 1997].

4.12 Radix Salvia miltiorrhizae (Red Sage Root, Danshen in Chinese)

Danshen is the root and rhizome of Salvia miltiorrhiza Bge. (Labiatae), mainly produced in Hebei, Shanxi, Inner Mongolia, Liaoning, and Jilin of China. The herb is collected in spring or autumn and dried in the sun. Traditinally, Danshen can be used in menstrual disorders, subcutaneous infection and insomnia by removing blood stasis, relieveing pain and easing the mind.

In photochemistry, at least 80 compounds have been separated and identified from Danshen, including lipophilic compounds and hydrophilic compounds. Tanshinone IIA and Salvianolic Acid B are the main component and are credited as criteria for quality control of

Danshen in China Pharmacopeia (Edition 2005).Danshen is one of the most popular herbs in China. It has been widely applied for many years to treat various diseases by its neuroprotective, antimicrobial, cardiovascular, hepatoprotective, antiinflammatory and immunomodulatory effects, especially in cardiovascular and cerebrovascular disease (Feng et al., 2010). In recent years, danshen and its active compounds also showed anticancer effects as mentioned follows.

The aqueous extract of Danshen can inhibit the proliferation of HepG2 cells (Jiang et al., 2005). Salvinal, a compound identified from aqueous extract, inhibiting tubulin polymerization, arresting the cell cycle at mitosis, and inducing apoptosis in multidrug-sensitive and -resistant human tumor cells (Chang et al., 2004). Another hydrophilic component Salvianolic acid B inhibits growth of head and neck squamous cell carcinoma in vitro and in vivo via inhibiting cyclooxygenase-2 expression (Hao et al., 2009). The chi-shen extract (CSE) from the water-soluble compounds of Salvia miltiorrhiza and Paeoniae radix shows anticancer effects which are related to the Bcl-2 family pathway and the activation of caspases-3 and -9 in HepG2 cells (Hu et al., 2007). Tanshinone IIA can induce apoptosis in HL60, CNE1, SPC-A-1, NB4, K562 and HepG2 cell lines, and the cytotoxicity partly through mitotic arrest or activation of capspase 3 (Yoon et al., 1999; Yuan et al., 2003; Lee et al., 2008; Zhou et al., 2008). Tanshinone IIA can inhibit the proliferation of non-small cell lung cancer A549 cells which is possibly by decreasing the MMP and inducing apoptosis due to the induction of a higher ratio of Bax/Bcl-2 (Chiu and Su 2010). Tanshinone I induces apoptosis, suppresses growth and invasion in MCF-7 and MDA-MB-231 breast cancer cell line, and its effect may be partly through activation of caspase 3 and regulation of some adhesion molecules, including intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). Tanshinone I also exerts anticancer effect via mediation of interleukin-8, Ras-mitogen-activated protein kinase, and Rac1 signaling pathways in highly invasive human lung adenocarcinoma cell line, CL1-5 and CL1-5-bearing severe combined immunodeficient mice (Lee et al., 2008). Furthermore, other tanshinones, such as sibiriquinone A, sibiriquinone B, cryptotanshinone, and dihydrotanshinone I possess the anticancer activity partly through inhibition of HIF-1 accumulation (Dat et al., 2007). Recentlly, a novel compound, acetyltanshinone IIA (ATA) was obtained from chemical modifications of tanshinone TIIA (TIIA) which shows a higher growth inhibition ability on breast cancer especially HER2 positive cells than normal cells and it inhibits xenografted tumor growth in mice due to significant reactive oxygen species (ROS) generation, Bax translocation to mitochondria, resulting in mitochondria damage, cytochrome c release, caspase-3 activation and apoptotic cell death (Tian et al., 2010).

Denshen has low toxicity and less side effects in clinical practice. LD50 of Danshen water extract for mice: 25.807 g/kg by oral administration. This LD50 value is equivalent to 3934 times the intended clinical human oral dosage (6.56 mg of Danshen extract/kg). Treating rats with an oral dose of 2500 mg/kg Danshen extract (400 times human oral dosage) for 90 days have been found to be nontoxic (Tianjin Talisco Pharmaceutical Group Co. Ltd., 1998).

5. Conclusion

Chinese medicine is an unique medical system, among which Chinese medicines have been used in main stream medical health care in China for years of thousands and have been accepted by many countries as an complemental and alternative medicine. On the other hand, Chinese medicines are also as a resource in new drug development for unmet medical

needs in some hard-to-cure diseases. In this chapter, we reviewed the recent progress of twelve representative Chinese medicines (Rhizoma coptidis, arsenic, Rhizoma Curcuma longae, Radis stephaniae tetrandrae, Radix tripterygii wilfordii, Radix scutellariae, Herba artemisiae annuae, Radix ginseng, Radix notoginseng, Radix astragali, Radix angelicae senensis and Radix salviae miltiorrhizae) on the anticancer cellular and molecular mechanisms, major active chemical ingredients and adverse effects. We noted that safety, quality control and sustainable development should be stressed in Chinese medicines research. On the other hand, research mainly focused on sigle Chinese medicines in the past decades, we should do more studies on composite fomulae in the future. 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 in the worldwide.

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