Review

DOI: 10.5582/ddt.2014.01032

A map describing the association between effective components of traditional Chinese medicine and signaling pathways in cancer cells *in vitro* and *in vivo*

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Summary **Cancer is the second leading cause of death by disease in the world. Chemotherapy is one of three major therapeutic methods for cancer treatment, but cancer cells gradually evolve resistance to chemotherapeutic reagents. For centuries, traditional Chinese medicine (TCM) was used to fight against cancer. In recent years, a number of effective component mechanisms of TCM have been increasingly illuminated. As we know, chemical structures of reagents decide or affect their activities on target pathways. Thus, we classified some antitumor-related TCM components reported in the last five years into thirteen groups by their chemical structures, such as, alkaloids, diterpenoids, triterpenes, sesquiterpenes, anthraquinones, benzoquinones, flavonoids, berbamines, xanthones, saponins, steroids, polysaccharides, and glycosides. In various cancer cell lines, these constituents target dozens of signaling pathways *in vitro* and *in vivo*. Among these components, there are three sets: *i*) mainly apoptosis-related groups, such as, alkaloids, diterpenoids, anthraquinones, berbamines, and xanthones, target pathways like the mitochondrial pathway, NF-κB pathway, p53 pathway and so on; *ii*) mainly proliferation, invasion and metastasis-related groups, such as, triterpenes, sesquiterpenes, polysaccharides, and glycosides, target pathways like the mTOR pathway, β-catenin pathway, ERK pathway and so on; *iii*) both apoptosis and proliferation, invasion and metastasis-related groups, such as benzoquinones, flavonoids, saponins, and steroids, target the pathways in *i*) and *ii*) synchronously. These will provide association information between TCM components and signaling pathways to promote studies on mechanisms of effective constituents, target drug development, and combinational chemotherapy. TCM could be alternative medicine for cancer treatment in the future.**

Keywords: Traditional Chinese medicine, signaling pathway, chemical structure, alternative medicine, combination therapy

1. Introduction

In 2008, approximately 12.7 million cancers were diagnosed (excluding non-melanoma skin cancers and other non-invasive cancers) (*1*), and in 2010 nearly 7.98 million people died. Cancers as a group account for approximately 13% of all deaths each year with the most common being: lung cancer (1.4 million deaths), stomach cancer (740,000 deaths), liver cancer (700,000 deaths), colorectal cancer (610,000 deaths), and breast cancer (460,000 deaths) (*2*). This makes invasive cancer the leading cause of death in the developed world and the second leading cause of death in the developing world. Over half of the cases occur in the developing world.

Chemoprevention is one of the major approaches for decreasing cancer morbidity and mortality (*3*). However, resistance to chemotherapy and molecular target therapies is becoming a big barrier for current cancer research. Because of the high cost of developing novel

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chemotherapeutic or targeted drugs, there is an emergent requirement for alternative medication.

It was reported that traditional Chinese medicine (TCM) had been widely applied for cancer care in China and there has been a great number of controlled clinical studies reported in Chinese papers (*4*). TCM uses a combinational medication of different natural components. To better understand the therapeutic effects of TCM, many efforts have been made to identify the constituents of TCM and to lift the veil of molecular mechanisms from it.

In recent years, a few reports suggested that certain kinds of chemical structures may relate to some corresponding cellular signaling pathways (*5*). Thus, we summarized the last five years' studies on TCM components functions on cancer cell signaling pathways and aimed at looking for association between chemical structure of TCM constituents and cancer cell signaling pathways.

2. Association between chemical structure of TCM constituents and cancer cell signaling pathways

Based on the last five years' papers on TCM components related cellular signal pathway research, the chemical structure of dozens of TCM constituents have been analyzed and relationships to signal pathways has been summarized (Table 1).

2.1. *Alkaloid*

Alkaloids are a group of naturally occurring chemical

Table 1. Components of TCM commonly used in cancer treatment

Components	Cell lines	Animals	Pathways	*Ref.*
Alkaloid	9KB, L1210, HeLa, MCF-7,HCT116, A549,MNNG/HOS,M21,A375, 95D	Mice	mTOR, NF-κB, p53, HIF-1α,FOXO3α, mitochondria,	*6-19*
Diterpenoid	β-TC-6,SGC996, NOZ,MDA-MB-231, SW620	Mice	PI3K/Akt,FAK,p38 MAPK, NF-κB,HIF-1α, mitochondria	*20-29*
Triterpene	HeLa,T24, HepG2, MDA-MB-231, HEK293, HCT15, CO115	Mice Zebrafish	NF-κB, angpt2/tie2, STAT3, β-catenin, EGFR, FAK-SRC-Paxillin	*30-39*
Sesquiterpene	HUVECs, MCF-7, MKN-45, A2780/CP70,MCAS	Mice	Akt/GSK3β, mTOR, Smad3,JNK,Notch-1,Snail/E-cadherin,	*40-44*
Anthraquinone	MCF-7,HeLa,MDA-MB-231,HepG2,U87,NPC-TW-039, NPC-TW-076	Mice	NF-κB, p53, MAPK, mitochondria,	*45-50*
Benzoquinone	HeLa,AGS,BXPC-3, PANC-1, ASPC-1, A549,NTHY-0RI 3-1 CL1-0, CL1-5, DU145,	Mice	NF-κB, PI3K/Akt, ERK1/2, mitochondria	*51-58*
Flavonoid	MDA-MB-231, MCF-7, T24, U87MG, U251MG, MHCC97H, AGS, A549, PC-3, A431, SKBr3, BGC-823, HT-29, 5637, A2780/CP70, OVCAR-3,	Mice	NF-κB, mTOR, p38 MAPK,mitochondria, ROS, TGF-β, ERK, p53, Rac1	*59-74*
Berbamine	HepG2, PLC/PRF/5, SK-Hep-1, SNU398, Bxpc-3, Panc-1, A2058, A375, G361, SK-MEL-28, U87, SK-MEL-5, Raji, L428, Namalwa, Jurkat, HCT116, HCT8, MCF-7, HUVECs	Mice	NF-κB,TGF-β/Smad, STAT3, JNK, mTOR, HIF-1α	*75-80*
Xanthone	HepG2,Hep3B, Huh-7,Bel7404, BGC-823, SGC-7901, SK-Hep-1, MIAPaCa-2, BxPC-3, PC-3	Mice	STAT3, ERK, JNK, mitochondria	*81-86*
Saponin	HL-60,T47D,HeLa, MDA-MA-231, MDA-MB-453, NCI-H157, SKOV3, NCI-H460, A549, MCF-7, SPCA-1, H1975, NCI-H446, NCI-H292, NCI-H69, HO-8910PM	Mice	JNK, p38 MAPK, mitochondria, mTOR, AIF, ROS, p53/p21, β-catenin	*87-95*
Steroid	HCCLM3, HepG2, A549,MDAMB-231,LNCaP,DU145,PC3,HL-60,MGc-803, SW620, HeLa, 4T1	Mice	Met/PI3K/Akt, STAT3, NF-κB, AKT/GSK3β/β-catenin, FAK/Rac1, MAPK	*96-104*
Polysaccharide	HT-29, LOVO, CL1-5,A549, Hca-F, 4T1, HL-60, U-2	Mice	ErbB, IGF-1R, TGFR/Smad7, NF-κB, ERK, death receptor,β-catenin, mitochondria	*105-113*
Glycoside	TEU-2, A549, H22, MCF-7, YD-10B	Mice	mTOR, MAPK, ERK, NF-κB, Rac1, β-catenin, mitochondria	*114-119*

compounds (natural products) that contain mostly basic nitrogen atoms. Alkaloids are produced by a large variety of organisms including bacteria, fungi, plants, and animals. They often have pharmacological effects and are used as medications, as recreational drugs, or in entheogenic rituals (*6*). The following are some TCM components which were reported in recent years.

Camptothecin, which is extracted from *Camptoteca acuminata Decne*, and its derivatives can inhibit cancer cell proliferation by suppressing DNA topoisomerase I by stabilizing certain intermediate complexes during DNA synthesis (*7*). It has been applied to 9KB (human oral epidermoid carcinoma cell line) and L1210 (human leukemia cell line). It also can induce p53-dependent DNA damage in renal cell carcinoma (*8*). In another report, camptothecin induces apoptosis through the hypoxia-inducible factor-1α (HIF-1α) pathway in HeLa (human cervix adenocarcinoma cell line) (*9*). In the HCT116 coloretctal cancer cell, camptothecin can induce apoptosis through the AMPK-TSC2-mTOR pathway (*10*).

Vinblastine, which is derived from *Vinca rosea* L., can arrest the cell cycle through inhibiting assembly of microtubules and binding to subunits of tubulin in S phase. Anticancer activity was assayed against MCF-7 (human breast cancer cell line) (*11*). An *in vitro* and *in vivo* study suggests a synergistic anticancer activity of a nanoliposomal C6-ceramide and vinblastine combination, potentially lead by an autophagy mechanism (*12*).

Berberine is a natural product extracted from roots of *Coptis chinensis* Franch which has been shown to have anticancer activities. In HCT116 (human colon cancer cell line), it suppresses proliferation *via* AMPK dependent inhibition of mTOR activity and induces apoptosis by AMPK dependent inhibition of NF-κB. *In vivo*, it also inhibits mTOR and activates caspase-3 cleavage (*13*). In A549 (human lung adenocarcinoma cell line), berberine inhibits proliferation and induces apoptosis of adenocarcinoma cells by activating the p38α MAPK signaling pathway followed by inducing p53 and FOXO3α (*14*).

Oxymatrine, the main constituent in the traditional Chinese herbal medicine *Sophora japonica*, has been reported to have antitumor properties. In human osteosarcoma MNNG/HOS cell line, oxymatrine induces mitochondria dependent apoptosis by inhibiting the PI3K/Akt pathway (*15*). In an *in intro* and *in vivo* experiment, oxymatrine shows an antiangiogenic effect on pancreatic cancer through inhibition of the NF-κB-mediated VEGF signaling pathway (*16*).

Matrine is a major active component in traditional Chinese medicine *Sophora flavescens*. It has been reported that matrine induces growth inhibition and apoptosis of M21 and A375 (human melanoma cell lines) by activating the PTEN pathway (*17*). Matrine also induces apoptosis of A549 and 95D (human lung cancer cell lines) *via* the PI3K/Akt/mTOR signaling pathway and down-regulation of inhibitor of apoptosis proteins (*18*). Another study reports that matrine inhibits the invasive activities of human osteosarcoma cells through down-regulation of the ERK/NF-κB pathway *in intro* and *in vivo* (*19*).

These alkaloid components can suppress proliferation, invasion, or apoptosis of cancer cells by the following pathways: *i*) AMPK/mTOR pathway; *ii*) MAPK/Akt/mTOR pathway; *iii*) NF-κB pathway; *iv*) p53 apoptosis pathway; *v*) HIF-1α pathway; *vi*) mitochondria-dependent pathway; and *vii*) FOXO3α pathway. The first three pathways are major signaling pathways activated by alkaloids from TCM.

2.2. *Diterpenoid*

The terpenoids are a large and diverse class of naturally occurring organic chemicals similar to terpenes, derived from five-carbon isoprene units assembled and modified in thousands of ways. Most are multicyclic structures that differ from one another not only in functional groups but also in their basic carbon skeletons. These lipids can be found in all classes of living things, and are the largest group of natural products (*20*). Diterpenoids, a member of the terpenoid family, with their twenty-carbon backbone constitute roughly a fourth of all known plant terpenoids, which currently are more than 12,000 (and counting) structures known. The followings are some TCM-derived diterpenoid components.

Andrographolide is a diterpenoid lactone derived from *Andrographis paniculata*. The combination of andrographolide and taxifolin inhibit proliferation and trigger apoptosis of breast cancer cells by disrupting microtubule dynamics and acitivating the spindle assembly checkpoint (SAC) (*21*). In other studies, andrographolide alone can inhibit proliferation of breast cancer cells and non-small cell lung cancer (NSCLC) cells by downregulating the PI3K/Akt pathway (*22,23*). NSCLC cells also can be suppressed by andrographolide through the HIF-1α pathway (*24*). In the β-TC-6 (human insulinoma cell line), andrographolide suppress growth of cancer cells through inhibition of the TLR4/NF-κB signaling pathway *in intro* and *in vivo* (*25*).

Oridonin is isolated from the plant *Rabdosia rubescens*. It can inhibit growth of prostate cancer cells by suppressing the NF-κB signaling pathway *in intro* and *in vivo* (*26*). In human gallbladder cancer cell lines SGC996 and NOZ, oridonin induces apoptosis and cell cycle arrest *via* the mitochondrial pathway (*27*). It is also reported to suppress invasion and metastasis of human breast cancer cell line MDA-MB-231 *in vitro* by decreasing the expression of MMPs and regulating the Integrinβ/FAK pathway *in vitro* (*28*).

Diterpenoid C is isolated from *Radix Curcumae* which is the dry root of Curcuma wenyujin. In a study on human colon adenocarcinoma cell line SW620,

diterpenoid C functions as an inhibitor of proliferation and inducer of apoptosis through the MAPK signaling pathway (*29*).

The diterpenoids can induce apoptosis and inhibit invasion of cancer cells *via* the following pathways: *i*) PI3K/Akt pathway; *ii*) p38 MAPK pathway; *iii*) NF-κB pathway; *iv*) HIF-1α pathway; *v*) mitochondria-dependant pathway; *vi*) FAK pathway; and *vii*) disrupting microtubule dynamics and acitivating SAC. The first three pathways are affected by most diterpenoids above and they have crosstalk between each other.

2.3. *Triterpene*

Triterpenes are terpenes consisting of six isoprene units and have the molecular formula $C_{30}H_{48}$. The pentacyclic triterpenes can be classified into lupane, oleanane or ursane groups. A notable pentacyclic triterpene is Boswellic acid.

Ganoderic acid is a triterpene derived from *Ganoderma lucidum*. It induces mitochondria-dependent apoptosis in human cervical carcinoma HeLa cells *in vitro* (*30*). Ganoderic acid can also inhibit growth and angiogenesis of human breast cancer cell line MDA-MB-231 by modulating the NF-κB signaling pathway (*31*). On the other hand, ganoderic acid can enhance chemosensitivity of human hepatocellular carcinoma (HCC) cell line HepG2 to cisplatin by inhibiting the JAK-STAT3 signaling pathway (*32*). This suggests that ganoderic acid can be used in combination with chemotherapeutic agents for cancer treatment.

Ursolic acid is a triterpene compound isolated from certain traditional medicinal plants, such as *Mirabilis jalapa*. Ursolic acid was proved to suppress the proliferation of colon cancer cell line HEK293 by promoting degradation of β-catenin (*33*). In Enrlich ascites carcinoma cell line, ursolic acid acts as an inducer of apoptosis through the mitochondrial signaling pathway *in intro* and *in vivo* (*34*), and in T24 human bladder cancer cells, it induces apoptosis *via* the Akt/NF-κB pathway (*35*). Ursolic acid also can induce cell death and modulate autophagy by the JNK pathway in the apoptosis-resistant human colon carcinoma cell line HCT15 and CO115 (*36*).

Ganoderiol A is a natural product isolated from traditional Chinese medicine *Ganoderma lucidum*. It inhibits migration and adhesion of highly metastatic breast cancer cell line MDA-MB-231 by suppressing the FAK-SRC-Paxillin cascade pathway (*37*).

The fruit of *Poncirus trifoliate* has been used as traditional medicine for many years, and 25-Methoxyhispidol A is derived from it. In MDA-MB-231 breast cancer cells, 25-Methoxyhispidol A suppresses cell growth through modulation of the EGFR/c-Src signaling pathway *in vitro* (*38*).

Friedelan-3-one and 29-hydroxyfriedelan-3-one are exacted from *Tripterygium wilfordii* which has been traditionally used as folk medicine for treatment of inflammatory diseases. They show antiangiogenic activity against vessel formation in the zebrafish model by inhibiting the angpt2/tie2 signaling pathway. (*39*)

The triterpenes above mainly fight against cancer cells *via* the following pathways: *i*) mitochondria pathway; *ii*) NF-κB pathway; *iii*) angpt2/tie2 signaling pathway; *iv*) JAK-STAT3 pathway; *v*) β-catenin pathway; *vi*) FAK-SRC-Paxillin cascade pathway; and *vii*) EGFR/c-Src pathway. The first three pathways are affected by more than two components.

2.4. *Sesquiterpene*

Sesquiterpenes are a class of terpenes that consist of three isoprene units and have the molecular formula $C_{15}H_{24}$. Like monoterpenes, sesquiterpenes may be acyclic or contain rings, including many unique combinations.

Dehydrocostus lactone is a TCM component derived from *Saussurea costus* (Falc.) Lipschitz. In human umbilical vein endothelial cells (HUVECs), it suppresses angiogenesis by inhibiting Akt/GSK3β and mTOR signaling pathways *in intro* and *in vivo* (*40*).

β-Elemene, a naturally occurring component isolated from *Curcumae Radix*, has been used as an antitumor drug for various cancers in China. It has been reported to be able to block epithelial-mesenchymal transition (EMT) in MCF-7, a human breast cancer cell line, by Smad3-mediated down-regulation of nuclear transcription factors (SNAI1, SNAI2, TWIST and SIP1) (*41*). In the same cell line, other research proves that β-elemene decreases cell invasion through up-regulation of E-cadherin expression (*42*). In research on gastric cancer stem-like cells, β-elemene is effective in attenuating angiogenesis by targeting Notch-1 *in intro* and *in vivo* (*43*). A study on a combination of β-elemene and cisplatin suggests that in resistant ovarian carcinoma cells β-elemene increases susceptibility to cisplatin by inactivating the JNK pathway (*44*).

These sesquiterpenes block proliferation and invasion of cancer cells by some different pathways as follows: *i*) Akt/GSK3β pathway; *ii*) mTOR pathway; *iii*) Smad3 pathway; *iv*) Snail/E-cadherin pathway; *v*) Notch-1 pathway; and *vi*) JNK pahway.

2.5. *Anthraquinone*

Anthraquinone, also called anthracenedione or dioxoanthracene, is an aromatic organic compound with formula $C_{14}H_8O_2$. Several isomers are possible, each of which can be viewed as a quinone derivative. The term anthraquinone, however, almost invariably refers to one specific isomer, 9,10-anthraquinone wherein the keto groups are located on the central ring.

Emodin, a naturally occurring anthraquinone component derived from *Polygoni cuspidati radix*, has

been reported to have anti-cancer and anti-inflammatory activities. In MCF-7 and MDA-MB-231 human breast cell lines, emodin leads to inhibition of proliferation through the ERα-MAPK/Akt-Cyclin D1/Bcl-2 signaling pathway (*45*). Emodin induces apoptosis of the HeLa human cervical cell line by activation of the mitochondria apoptotic pathway (*46*). Cancer cell apoptosis also can be induced by emodin in the HepG2 human HCC cell line through activation of the p53 pathway and inhibition of the NF-κB/p65 pathway (*47*).

Aloe emodin, one of the active compounds isolated from *Aloe vera* leaves, plays an important role in the regulation of cell growth and death. It induces cell cycle arrest and apoptosis *via* the mitochondria dependent signaling pathway in human U87 malignant glioma cells (*48*). Another study proved that aloe emodin induces invasive inhibition of NPC-TW 039 and NPC-TW 076 human nasopharyngeal carcinoma cell lines by decreasing expression levels of MMP-2 through the p38 MAPK/NF-κB signaling pathway (*49*).

2-methyl-1,3,6-trihydroxy-9,10-anthraquinone is one of the major constituents derived from the TCM *Rubia yunnanensis* which exhibits inhibitory activity of proliferation of several human cancer cell lines. In the HeLa human cervical cancer cell line, 2-methyl-1,3,6-trihydroxy-9,10-anthraquinone was demonstrated to induce cell cycle arrest and apoptosis of cancer cells through the p53/p21/Cdc2-cyclin B1 signaling pathway (*50*).

These anthraquinones above show antitumor activities through several pathways: *i*) mitochondria-dependent pathway; *ii*) NF-κB pathway; *iii*) MAPK/Cyclin D1/Bcl-2 pathway; *iv*) p53 pathway; and *v*) Cdc2/Cyclin B1 pathway. The first two pathways play a role as frequent targets.

2.6. *Benzoquinone*

Benzoquinone is a quinone with a single benzene ring, of which there are only two members: *i*) 1,4-Benzoquinone, most commonly; and *ii*) 1,2-Benzoquinone, less commonly.

Rhinacanthone, a main bioactive component derived from *Rhinacanthus nasutus* KURZ, has been reported to possess antitumor activities. Recent research demonstrates that rhinacanthone leads to apoptosis of HeLa human cervical carcinoma cells through the mitochondria-dependent signaling pathway.

Shikonin, a natural product derived from the Chinese medical herb *Lithospermum erythrorhizon*, has been widely used as a traditional Chinese medicine for thousands of years. In the BXPC-3 human pancreatic carcinoma cell line, it promotes autophagy through the PI3K/Akt signaling pathway (*51*). In another human pancreatic carcinoma study, PANC-1, BXPC-3, and ASPC-1 cell lines were employed. Shikonin is combined with gemcitabine, a nucleoside analog used as chemotherapy, and the combination group is demonstrated to suppress tumor growth *in vitro* and *in vivo* through the NF-κB pathway (*52*). In a human gastric cancer study, shikonin induced cell cycle arrest of the AGS cell line by the early growth response 1 (Egr1)/p21 signaling pathway (*53*). In A549 lung cancer cell line, Shikonin attenuates adhesion of cells to extracellular matrix and metastasis through inhibition of the ERK1/2 signaling pathway (*54*). In the NTHY-0RI 3-1 human papillary thyroid carcinoma cell line, shikonin plays a role in inducing apoptosis through the mitochondrial pathway (*55*).

Tanshinone I, a bioactive constituent of *Salvia miltiorrhiza* Bunge, has been used in China for thousands of years to treat various diseases, such as heart disease, hepatitis, and cancer. In A549, CL1-0, and CL1-5 cell lines, tanshinone I inhibits cancer progress by blocking the cell cycle pathway and VEGF protein *in vitro* and *in vivo* (*56*). In the DU145 human prostate cancer cell line, tanshinone I induces apoptosis of cancer cells by activating the mitochondrial pathway (*57*). In a paper published in 2008, Tanshinone I was reported to suppress proliferation of NSCLC cells through the NF-κB pathway (*58*).

These benzoquinones target several pathways: *i*) mitochondrial pathway; *ii*) NF-κB pathway; *iii*) PI3K/Akt pathway; *iv*) ERK1/2 pathway; and *v*) cell cycle pathway. The first two pathways are targets of all of these benzoquinones.

2.7. *Flavonoid*

Flavonoids are a class of plant secondary metabolites. Flavonoids were referred to as Vitamin P from the mid-1930s to early 50s, but the term has since fallen out of use. Chemically, they have the general structure of a 15-carbon skeleton, which consists of two phenyl rings (A and B) and a heterocyclic ring (C). This carbon structure can be abbreviated C6-C3-C6. Flavonoids have been reported to possess various therapeutic effects for inflammation, cancer, and cardiovascular diseases.

Baicalein (5,6,7-trihydroxyflavone) is a flavone, a type of flavonoid, originally isolated from the roots of *Scutellaria baicalensis*. It has been reported to inhibit migration and invasion of human gastric cancer cells by suppressing the TGF-β signaling pathway (*59*). In the human breast carcinoma cell line MDA-MB-231, baicalein shows its ability to induce autophagic cell death *via* activation of the AMPK/ULK1 pathway and inhibition of the mTOR pathway (*60*). Baicalein also can lead to apoptosis of MCF-7 human breast cancer cells and T24 human bladder cancer cells through a decrease of the reactive oxygen species (ROS)-dependent apoptosis pathway and mitochondrial-dependent caspase activation pathway respectively (*61,62*). A study on invasion of glioma cells shows

that baicalein attenuates the invasion of U87MG and U251MG cell lines by inhibition of the activity of the p38 MAPK signaling pathway (*63*). Through MAPK family pathways, baicalein also is reported to suppress the invasion and metastasis of the MHCC97H human HCC cell line *via* down-regulation of the ERK signaling pathway (*64*).

Quercetin, a flavonol, is a flavonoid, in other words, a plant pigment with a molecular structure like or derived from flavone. In AGS human gastric cancer cells, quercetin induces apoptosis through inhibition of the p38 MAPK signaling pathway (*65*). In combination with trichostatin A, a eukaryotic cell cycle inhibitor, quercetin enhances treatment effects by inhibiting proliferation of A549 human NSCLC cells through the p53 signaling pathway *in vitro* and *in vivo* (*66*). In a study on human prostate tumors, quercetin was shown to inhibit angiogenesis by targeting the VEGFR-2 mediated mTOR signaling pathway *in vitro* and *in vivo* (*67*). Quercetin has been reported to induce apoptosis of human prostate cancer PC-3 cells through endoplasmic reticulum (ER) stress and the mitochondrial apoptotic signaling pathway (*68*).

Icariin is a flavonol glycoside, a type of flavonoid. It is the 8-prenyl derivative of kaempferol 3,7-O-diglucoside. The compound is derived from several species of plants belonging to the genus *Epimedium Berberidaceae*. It induces apoptosis of A431 human epidermoid carcinoma cells by inhibiting the EGFR pathway (*69*). Similarly, other research also proves that icariin inhibits proliferation of SKBr3 breast cancer cells *via* the EGFR-MAPK signaling pathway (*70*). In the BGC-823 human gastric cancer cell line, icariin exterts negative effects on invasion and migration through the Rac1 pathway (*71*).

Kaempferol is a natural flavonol, a type of flavonoid, that has been isolated from tea, broccoli, *Delphinium*, Witch-hazel, grapefruit, grapes, and other plant sources. It promotes apoptosis of HT-29 human colon cancer cells through activating cell surface death receptors and the mitochondrial pathway (*72*). In a recent paper, it was revealed that kaemperol attenuates the growth of 5637 and T24 human bladder cancer cells by inhibition of the c-Met/p38 MAPK signaling pathway *in vitro* and *in vivo* (*73*). The antitumor activity of kaempferol also has been shown in OVCAR-3 and A2780/CP70 human ovarian cancer cell lines, it suppresses expression of VEGF and angiogenesis by inhibiting the ERK-NF-κB pathway (*74*).

The above flavonoids play an efficient role against cancer cells by targeting various pathways: *i*) mTOR pathway; *ii*) mitochondrial pathway; *iii*) p38 MAPK pathway; *iv*) NF-κB pathway; *v*) TGF-β pathway; *vi*) ROS-dependant pathway; *vii*) ERK pathway; *viii*) p53 pathway; and *ix*) Rac1 pathway. MAPK pathway, mTOR pathway, the mitochondrial pathway, and NF-κB pathway all are inhibited by at least half of the listed flavonoids. That may suggest there is a certain association between these signaling pathways and flavonoids.

2.8. *Berbamine and its structural analogues*

Berbamine is a natural bisbenzylisoquinoline product derived from traditional Chinese herbal medicine *Berberis amurensis* and has been used to treat inflammatory and other diseases for centuries. In HepG2, PLC/PRF/5, SK-Hep-1, and SNU398 cells, berbamine plays a role in blocking the Ca^{2+} channel through inhibition of Ca^{2+}/calmodulin-dependent protein kinase II (introduction). In Bxpc-3 and Panc-1 human pancreatic cancer cell lines, berbamine can enhance antitumor activity of gemcitabine through activating the TGF-β/Smad pathway (*75*). A derivative of berbamine is reported to induce apoptosis of A2058, A375, G361, SK-MEL-28, and SK-MEL-5 human melanoma cell lines *via* inhibition of the jak2/STAT3 signaling pathway (*76*). Another berbamine derivative was proved to inhibit cell viability and lead to apoptosis of the U87 human glioblastoma cell line through up-regulation of the miRNA-4284 and JNK/AP-1 signaling pathway (*77*). 4-Chlorobenzoyl berbamine, a derivative of berbamine, was demonstrated to inhibit proliferation and induce apoptosis of Raji, L428, Namalwa, and Jurkat lymphoma cell lines through the PI3K/Akt and NF-κB pathway (*78*).

Dauricine, a natural product isolated from the rhizome of *Menispermum dauricum* DC, has been found to have antiarrhythmic and anti-inflammatory effects. It was proved to suppress proliferation and invasion and induce apoptosis of HCT116 and HCT8 human colon cancer cells by blocking the NF-κB signaling pathway (*79*). In the MCF-7 human breast cancer line and HUVECs human umbilical vein endothelial cells, dauricine plays a role in inhibiting angiogenesis of cancer cells by blocking the PI3K/Akt/mTOR pathway and HIF-1α pathway (*80*).

In brief, berbamine, its derivatives, and its analogues stand up to cancer cells through the following pathways: *i*) TGF-β/Smad pathway; *ii*) jak2/STAT3 pathway; *iii*) JNK/AP-1 pathway; *iv*) PI3K/Akt/mTOR pathway; *v*) NF-κB pathway; and *vi*) HIF-1α pathway. The PI3K/Akt/mTOR pathway and NF-κB pathway are both targeted by these components.

2.9. *Xanthone*

Xanthone is an organic compound with the molecular formula C13H8O2. It can be prepared by the heating of phenyl salicylate. Up to now, over 200 xanthones have been identified.

1,3,5-Trihydroxy-13,13-dimethyl-2H-pyran [7,6-b] xanthone (TDP), is isolated from the traditional Chinese medicinal herb *Garcinia oblongifolia*. Research on

this component is focused on human hepatocellular carcinoma. In this research, TDP is reported to induce apoptosis of cells by targeting the heat shock protein 27 (Hsp27) related signaling pathway (*81*). In another study, TDP was proved to lead to apoptosis of cells through activation of the mitochondrial signaling pathway (*82*).

α-Mangostin, a main xanthone component isolated from the pericarp of mangosteen (*Garcinia mangostana* Linn), possesses unique biological activities, including antioxidant, antitumor and anti-inflammatory effects. It has been identified to be able to increase apoptosis of BGC-823 and SGC-7901 human gastric adenocarcinoma cell lines by blocking the STAT3 siganaling pathway (*83*). In human hepatoma SK-Hep-1 cells, α-mangostin leads to mitochondrial dependent apoptosis *via* inhibition of the p38 MAPK signaling pathway (84). In MIAPaCa-2 and BxPC-3 human pancreatic cancer cell lines, α-mangostin can suppress the invasion and metastasis of pancreatic cancer cells by decreasing MMP-2 and MMP-9 expression, increasing E-cadherin expression and inhibiting the ERK signaling pathway (*85*). In the PC-3 human prostate carcinoma cell line, α-mangostin can also inhibit metastasis of cancer cells through inhibition of MMP-2 and MMP-9 *via* the JNK signaling pathway (*86*).

These xanthones mainly target the following pathways: *i*) mitochondrial pathway; *ii*) STAT3 pathway; *iii*) ERK pathway; and *iv*) JNK pathway. The mitochondrial pathway is targeted more frequently.

2.10. *Saponin*

Saponins are a class of chemical compounds found in particular abundance in various plant species. More specifically, they are amphipathic glycosides grouped phenomenologically by the soap-like foaming they produce when shaken in aqueous solutions, and structurally by having one or more hydrophilic glycoside moieties combined with a lipophilic triterpene derivative.

Dioscin, a plant steroidal glycoside isolated from *Polygonatum zanlanscianense* pump, exhibits cytotoxicity against a number of human malignant cell lines. In human myeloblast leukemia HL-60 cells, dioscin induces apoptosis of cancer cells by activating p38 MAPK and JNK through the caspase dependent mitochondrial signaling pathway (*87*). In MDA-MA-231, MDA-MB-453, and T47D human breast cancer cell lines, dioscin induces cell death through the apoptosis inducing factor (AIF) signaling pathway (*88*).

Ophiopogonin B (OP-B) is a bioactive component of Radix Ophiopogon Japonicus, which is often used in Chinese traditional medicine to treat pulmonary disease. In a paper published in Chinese, OP-B was proved to increase the autophage of human HeLa cells through repression of the Akt/mTOR signaling pathway (*89*). In human NSCLC cell lines NCI-H157 and NCI-H460, OP-B was proved to induce autophage of cancer cells *via* inhibition of the PI3K/Akt signaling pathway (*90*).

Saikosaponin, a naturally occurring compound isolated from *Bupleurum radix*, has been shown to exert anti-cancer activity in several cancer cell lines. In HeLa and Siha cervical cancer cell lines, SKOV3 ovarian cancer cell line, and A549 NSCLC cell line, combination administration of saikosaponin and cisplatin can sensitize cancer cells to cisplatin through the ROS-mediated apoptotic pathway (*91*). In MDA-MB-231 and MCF-7 human breast cancer cells, saikosaponin increases apoptosis through the p53/021 dependant pathway (*92*).

Periplocin is a natural product derived from *Cortex periplocae*. It is demonstrated to suppress proliferation and induce apoptosis of SW480 human colon carcinoma cells through the β-catenin/Tcf signaling pathway *in vitro* and *in vivo* (*93*). In human lung cancer cell lines A549, SPCA-1, H1975, NCI-H446, NCI-H460, NCI-H292 and NCI-H69, periplocin can inhibit proliferation and induce apoptosis of cancer cells by the Akt and ERK signaling pathway *in vitro* and *in vivo* (*94*).

Polyphyllin I, a component derived from *Rhizoma Paridis Chonglou*, was proved to suppress proliferation and metastasis of human ovarian cancer cell line HO-8910PM by activating the JNK signaling pathway (*95*).

Collectively, the above saponins fight against cancers by targeting the following pathways: *i*) p38 MAPK pathway; *ii*) JNK pathway; *iii*) mitochondrial pathway; *iv*) AIF pathway; *v*) mTOR pathway; *vi*) ROS dependant pathway; *vii*) p53/p21 pathway; *viii*) β-catenin/Tcf pathway; and *ix*) ERK pathway

2.11. *Steroid*

A steroid is a type of organic compound that contains a characteristic arrangement of four cycloalkane rings joined to one another.

Bufalin is a major bioactive component of Venenum Bufonis, a traditional Chinese medicine obtained from the skin and parotid venomglands of toads. In a EGFR mutant lung cancer cell line, it was proved to reverse HGF-induced EGFR-TKIs resistance by blocking the Met/PI3K/Akt signaling pathway (*96*). In human hepatoma cell lines HCCLM3 and HepG2, bufalin plays a role in suppressing proliferation, migration, invasion and adhesion of hepatoma cells inhibition of the AKT/GSK3β/β-catenin/E-cadherin signaling pathway (*97*). There are a number of research reports on the apoptosis effect of bufalin. In lung cancer cells, breast cancer cells, prostate cancer cells, hepatocellular carcinoma cells, gastric cancer cells, and leukemia cells, bufalin was demonstrated to induce apoptosis through the NF-κB pathway and mitochondrial pathway (*98*). Bufalin was also proved to increase apoptosis of SW620 human

colon cancer cells *via* inhibition of the jak/STAT3 signaling pathway (*99*).

Bufotalin, a major compound in toad venom, was demonstrated to sensitize the death receptor-induced apoptosis of HeLa cells by the STAT1-dependent signaling pathway (*100*).

Bufadienolide, a major class of biologically active compounds derived from the traditional Chinese medicine ChanSu, was proved to be a sensitizer of death receptor TRAIL through inhibition of the STAT3/Mcl-1 pathway (101). Arenobufagin, a natural bufadienolide from toad venom, increases apoptosis and autophagy of HepG2 human hepatocellular carcinoma cells by inhibiting the PI3K/Akt/mTOR signaling pathway (*102*).

Cucurbitacin E, a natural compound derived from the climbing stem of *Cucumis melo* L., was previously shown to have antioxidant and antitumor activities. In MDA-MB-231 and 4T1 human breast cancer cells, cucurbitacin E suppresses breast tumor metastasis *via* inhibition of the Src/FAK/Rac1/MMP pathway (*103*). In PC3 and HUVEC cells, cucurbitacin E restrains tumor angiogenesis *via* inhibition of VEGFR2-mediated Jak/STAT3 and MAPK signaling pathways (*104*).

These steroids are able to suppress proliferation or induce apoptosis of cancer cells by signaling pathways as follows: *i*) Met/PI3K/Akt pathway; *ii*) AKT/GSK3β/β-catenin/E-cadherin pathway; *iii*) NF-κB pathway; *iv*) mitochondrial pathway; *v*) STAT3 pathway; *vi*) STAT1 pathway; *vii*) Src/FAK/Rac1/MMP pathway; and *viii*) MAPK pathway. Based on this research, the main effect of steroids is to induce apoptosis of cancer cells.

2.12. *Polysaccharide*

Polysaccharides are polymeric carbohydrate molecules composed of long chains of monosaccharide units bound together by glycosidic linkages and on hydrolysis give the constituent monosaccharides or oligosaccharides. They range in structure from linear to highly branched.

Laminarin, a storage glucan (a polysaccharide of glucose) found in brown algae *Laminaria digitata*, is used in traditional Chinese medicine, and has been shown to have several biological activities, including anticancer activities. In HT-29 human colon cancer cells, it suppresses tumor cell proliferation through the ErbB signaling pathway (*105*). In human colon cancer LOVO cells, laminarin reveals an effect on induction of apoptosis through the mitochondrial signaling pathway (*106*). In another human colon cell line HT-29, laminarin was proved to induce apoptosis of cancer cells by regulating the insulin-like growth fator-IR (IGF-1R) signaling pathway (*107*). In the same cell line LOVO, laminarin was demonstrated by another research group to increase apoptosis of cancer cells by activating the death receptor (DR) signaling pathway(*108*).

Fucoidan is a sulfated polysaccharide found mainly in various species of brown algae and brown seaweed. In human NSCLC cell lines CL1-5 and A549, fucoidan decreases tumor proliferation *via* the TGFR/Smad7/Smurf2 pathway. Meanwhile, fucoidan reduces tumor size in LLC1-xenograft male C57BL/6 mice (*109*). In mouse hepatocarcinoma Hca-F cells, fucoidan can suppress tumor cell growth, adhesion, invasion, and metastasis through the NF-κB pathway and ERK pathway *in vitro* and *in vivo* (*110*). In 4T1 mouse breast cancer cells, fucoidan was proved to inhibit cancer cell growth by blockage of the Wnt/β-catenin signaling pathway *in vitro* and *in vivo* (*111*).

Blazei polysaccharides, polysaccharides extracted from the fungus *Agaricus blazei*, was demonstrated to induce apoptosis of human leukemia HL-60 cells *via* the mitochondrial signaling pathway (*112*). Another polysaccharide from pomegranate peels also induces apoptosis of U-2 human osteosarcoma cells through the mitochondrial signaling pathway (*113*).

These polysaccharides stand up to cancers by targeting the following pathways: *i*) mitochondrial pathway; *ii*) ErbB pathway; *iii*) IGF-1R pathway; *iv*) DR pathway; *v*) TGFR/Smad7/Smurf2 pathway; *vi*) NF-κB pathway; *vii*) ERK pathway; and *viii*) Wnt/β-catenin pathway. The mitochondrial pathway is the main target for polysaccharides.

2.13. *Glycoside*

Glycoside is a molecule in which a sugar is bound to another functional group *via* a glycosidic bond. Glycosides play numerous important roles in living organisms. Many plants store chemicals in the form of inactive glycosides. These can be activated by enzyme hydrolysis, which causes the sugar part to be broken off, making the chemical available for use.

Salidroside (Rhodioloside) is a glucoside of tyrosol found in the plant *Rhodiola rosea*. In TEU-2 human bladder epithelial cells, salidroside inhibits the growth of cancer cells by the blockage of the mTOR pathway (*114*). In the A549 NSCLC cell line, salidroside decreases tumor cell proliferation *via* inhibition of the ROS/p38 signaling pathway (*115*).

Gastrodin, a natural product isolated from *Gastrodia elata* Blume, was demonstrated to repress the growth of H22 murine ascetic hepatoma cells by inhibiting the NF-κB signaling pathway (*116*). Stevioside, a diterpene glycoside found in the leaf of *Stevia rebaudiana*, was reported to induce ROS-mediated apoptosis of MCF-7 cells *via* the mitochondrial pathway (*117*). Fomitoside-K, a biologically active component isolated from a mushroom *Fomitopsis nigra*, also can increase apoptosis of YD-10B human oral squamous cells through the mitochondrial pathway (*118*). In A549 lung cancer cells, oleifolioside B, a cycloartane-

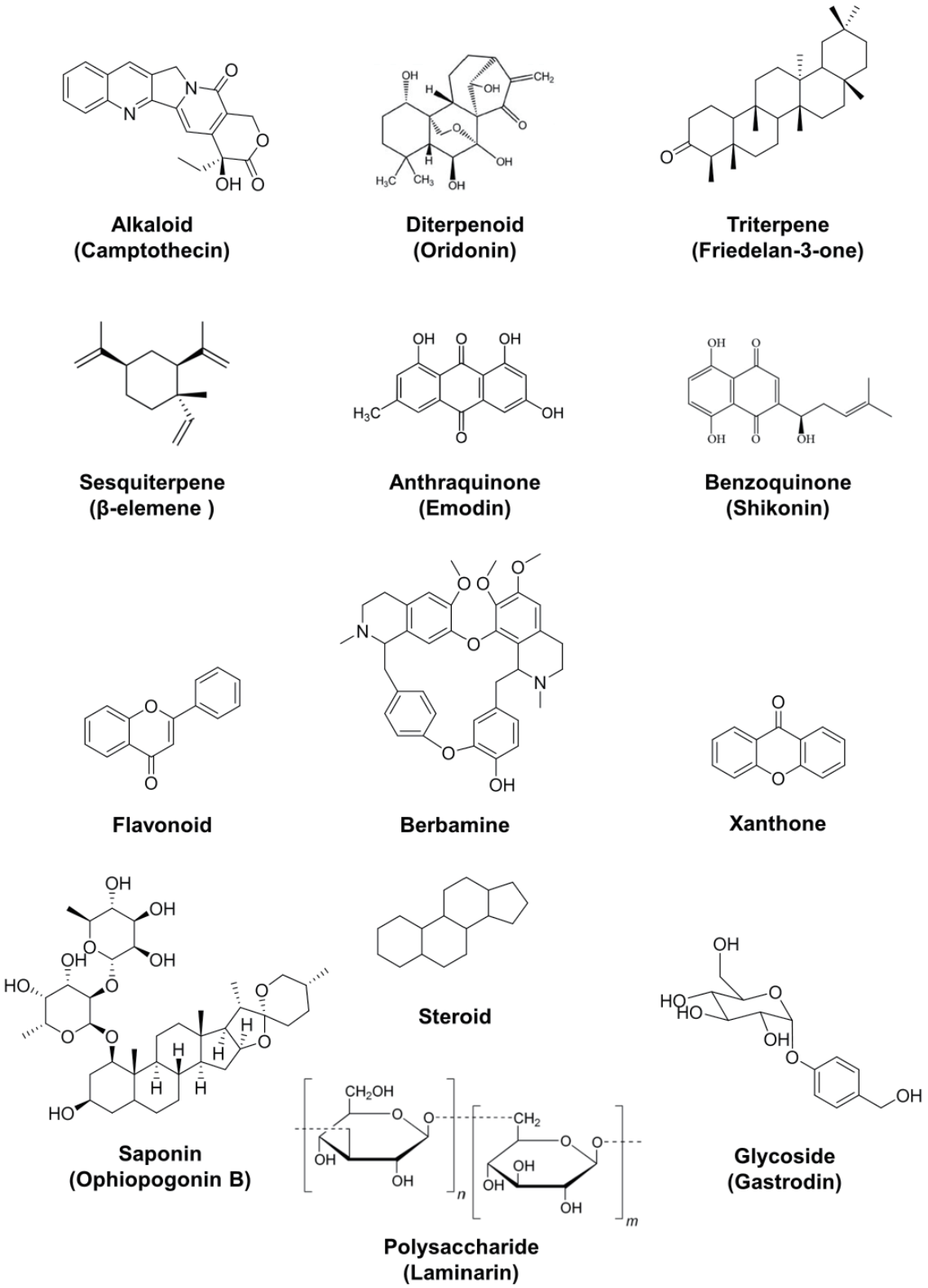

Figure 1. The typical chemical structures of TCM components.

type triterpene glycoside isolated from *Dendropanax morbifera* Leveille, promotes apoptosis through targeting the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway which can antagonize the NF-κB pathway (*119*). Periplocin and icariin which were mentioned above also belong to the glycoside family.

Summarily, these glycosides functions on cancer cells through signaling pathways as follows: *i*) mitochondrial pathway; *ii*) mTOR pathway; *iii*) MAPK pathway; *iv*) ERK pathway; *v*) NF-κB pathway; *vi*) β-catenin pathway; and *vii*) Rac1 pathway. The mitochondrial pathway is more common as a therapeutic target.

2.14. *Planar conformation and cell cycle arrest*

Based on several recent papers, a planar conformation could enhance the potency of the compound to intercalate into free DNA, and subsequently prevent DNA cleavage by DNA topoisomerase I (P1245) (120). For example, camptothecin has a planar pentacyclic ring structure that contains a pyrrolo [3,4-β]-quinoline moiety, conjugated pyridone moiety and one chiral center at position 20 within the alpha-hydroxy lactone ring with (S) configuration. Its planar structure is considered to be one of the most important factors in topoisomerase inhibition (P3,6) (*9*).

Among the TCM components mentioned above, many of them possess a planar conformation: aloe emodin, 2-methyl-1,3,6-trihydroxy-9,10-anthraquinone, shikonin, tanshinone I, 1,3,6,7-tetrahydroxyxanthone, 1,3,5-trihydroxy-13,13- dimethyl-2H-pyran [7,6-b] xanthone, and camptothecin.

3. Conclusion

In recent times, cancers have had the second highest mortality among all diseases. Although chemotherapy is acknowledged as one of the most effective therapeutic methods for cancers, it faces serious side effects and increasing drug resistance. For centuries, traditional Chinese medicine (TCM) was used to treat cardiac disease, diabetes, inflammation, cancer and so on. As the mechanisms of TCM remain poorly understood, more and more studies focus on research of the mechanisms of TCM *in vitro* and *in vivo*. Here, the components isolated from TCM are classified into several groups by their chemical structure (Figure 1) and corresponding cellular

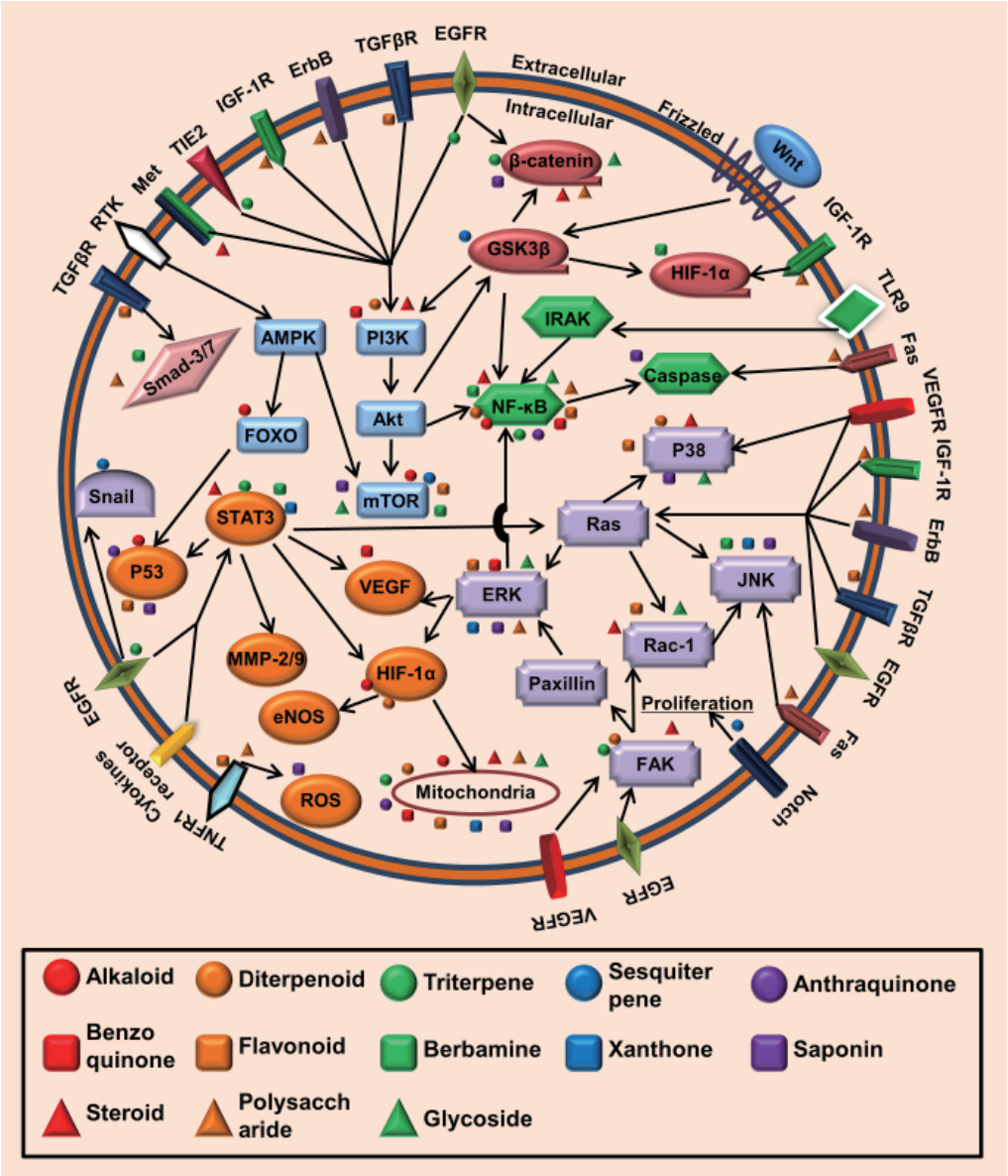

Figure 2. A map of association between TCM components and signaling pathways of cancer cells. In this map, the net of signaling pathways, which were reported to be affected by TCM components, are described and components are put around corresponding elements in the form of particles with various colors and shapes.

signaling pathways are summarized (Figure 2).

Based on the summary above, the veil over some characteristics has been lifted. First, the polysaccharide group mainly targets the cell surface receptors and induces a wider intracellular response, such as the ErbB pathway, IGF-1R pathway, DR pathway, TGF-β pathway, EGFR pathway, and angpt2/tie2 pathway. Second, the mitochondrial pathway and NF-κB pathway are the major targets for almost all of the groups. Targeting these two pathways leads to apoptosis of cancer cells. Meanwhile, apoptosis effects can be induced by other pathways, like the p53 pathway, HIF-1α pathway, ROS pathway, p38 MAPK pathway, FOXO3α pathway, DR pathway and so on. Maybe the combination of these different pathways can avoid drug resistance and make TCM a potential alternative medicine. Third, the mTOR signaling pathway is targeted by half of the component groups to inhibit proliferation, invasion and metastasis of cancer cells. There also are alternative pathways, such as the ERK pathway, β-catenin pathway, FAK pathway, Smad pathway, and so on. Fourth, in several studies, a combination of TCM components and existing chemotherapeutic agents could yield a better antitumor effect, such as vinblastine and nanoliposomal C6-ceramide, androgarpholide and taxifolin, ganoderic acid and cisplatin, β-elemene and cisplatin, shikonin and gemcitabine, quercetin and trichostatin A, and saikosaponin and cisplatin. Fifth, various component groups are oriented towards different pathways. Some of them focus more on apoptosis-related pathways, such as alkaloids, diterpenoids, anthraquinones, berbamines, and xanthones. While some of them concern more proliferation, invasion and metastasis-related pathways, such as triterpenes, sesquiterpenes, polysaccharides, and glycosides. Other components focus on both aspects, such as benzoquinones, flavonoids, saponins, and steroids. The more targets the components can attack, maybe the better antitumor effects they can achieve.

From the information above, it suggests there may be a certain association between some chemical structures and specific signaling pathways. However, there still are some uncertainties. First, although some components share the same core ring structure, various modifications make for different targeting pathways and cellular activity changes. Second, most research groups focus on several major signaling pathways, and association between TCM components and other pathways is short of enough data support. Third, information about chemical structural association between TCM components and targets is in short supply. In spite of this, studies on associations between TCM components and signaling pathways will shed light on future medicine development and administration. In the first place, the research mechanism of components will help identify the mechanisms of TCM. Secondly, associations between TCM components and pathways will provide some clues for target drug development. Third, this will provide a big picture of association between components and pathways for antitumor TCM studies. Finally, this research will provide evidence for combinational therapies using TCM and clinical chemotherapeutic drugs. Based on the advantages above, TCM could be widely used as alternative medicine for cancer therapies.

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(Received June 25, 2014; Revised July 29, 2014; Accepted August 5, 2014)