

## Research Advances in the Intervention of Inflammation and Cancer by Active Ingredients of Traditional Chinese Medicine

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Received, December 28, 2015; Revised, February 9, 2016; Accepted, February 11, 2016; Published, February 11, 2016.

**ABSTRACT** - A large body of evidence has shown that inflammation and cancer are strongly related. Thus anti-inflammatory agents have been investigated for cancer prevention and treatment in preclinical and clinical studies, including the nonsteroidal anti-inflammatory drugs (NSAIDs) and traditional Chinese medicine (TCM). In TCM, there exist a wide range of biologically active substances, such as saponins, flavonoids, alkaloids, polysaccharides, polyphenols, phenylpropanoids, and quinones. Many of these active ingredients have been reported to inhibit inflammation, activate inflammatory immune response, and/or inhibit cancer cell proliferation and tumor growth. Given the potential role of inflammation in cancer initiation and progression, the inflammatory tumor microenvironment, the cross-talks between inflammatory and cancer cells, and multitargeting activities of some TCM compounds, we summarize the current knowledge on the anti-inflammatory and anti-cancer properties of ingredients of TCM together with their underlying mechanisms in an integrated way. We hope to provide a reliable basis and useful information for the development of new treatment strategies of inflammation and cancer comprehensively using TCM and their active ingredients.

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### INTRODUCTION

The link between inflammation and cancer was first suggested by Virchow in 1863 (1) and has well been demonstrated by a large body of epidemiological research (1-7). In particular, it has been shown that cancer morbidity can be reduced by suppressing chronic inflammation in precancerous lesions or susceptible populations.

With increased understanding of the tumor origin and relevant inflammation, researchers have now started to focus on inflammatory factors in tumor microenvironment (TME) and identify new ways of treating tumors (8-15). For example, tumor necrosis factor (TNF) blockers (11), non-steroidal anti-inflammatory drugs (NSAIDs) (12-14), as well as chemotactic factor antagonists are used in tumor therapy (15). In recent decades, the active ingredients of TCM have gained increasing attention to their applications in the treatment of inflammatory diseases, the prevention of inflammation-associated cancer risk, and the treatment of various cancers, which has spanned from preclinical investigations to clinical trials (16-25). Here we review findings on the active ingredients of TCM that mediate inhibition

of inflammation and tumor growth. Owing to a vast number of ingredients in TCM and unclear pharmacological mechanisms for many of them, in this review we only select representative ingredients whose mechanisms of actions have been rigorously investigated. We hope that this review can provide useful information and stimulate new ideas on the treatment strategies of inflammation and cancer comprehensively using TCM and their active ingredients.

### INFLAMMATION AND TUMOR

In the TME, inflammatory cells, chemokines and cytokines promote the growth and metastasis of tumor cells, genetic mutations, and angiogenesis. Several exogenous and endogenous pathways define the complex relationship between inflammation and tumor (Figure 1) (26-35).

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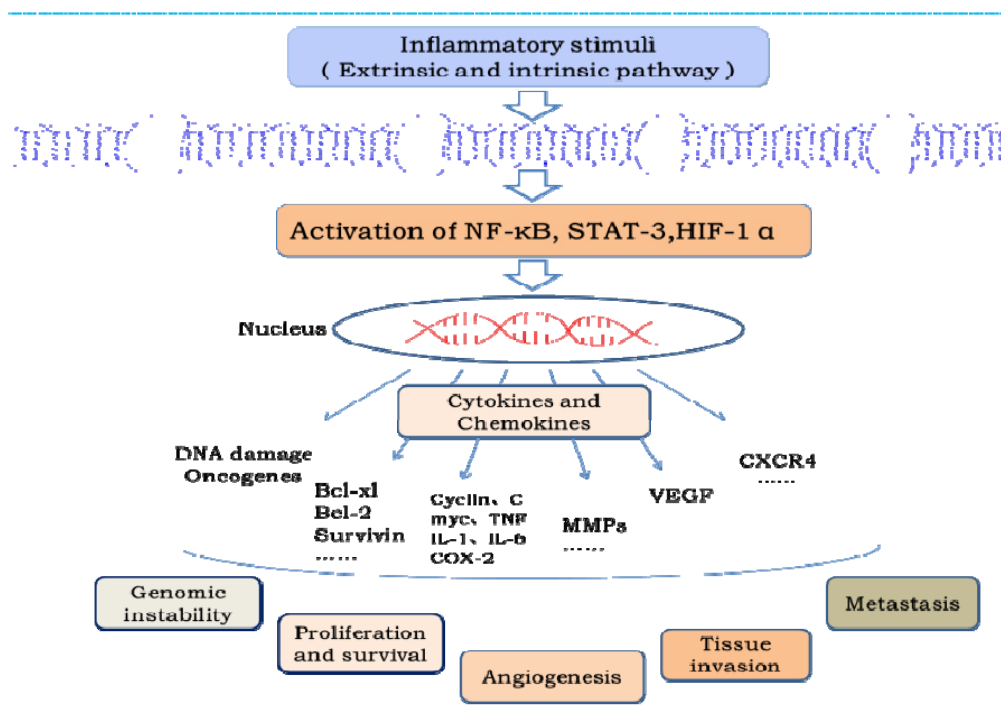
The exogenous pathway is induced by inflammation, such as in the inflammatory intestinal diseases. In endogenous pathways, activation of oncogenes, such as RET/PTC, RAS and MYC, causes expression of inflammation-related factors, creating an inflammatory microenvironment (27-29).

Tumor-related inflammatory factors include transcription factors, e.g. nuclear factor- $\kappa$ B (NF- $\kappa$ B), chemokines, and cytokines, e.g. tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) (30-32). NF- $\kappa$ B is an important regulator of natural immunity and inflammation, and is also an endogenous tumor factor (33). TNF- $\alpha$  is an inflammatory cytokine with a variety of biological activities (30) that participates in the activation of immune response, mediation of systemic inflammation, and induction of tumorigenesis. Signal transducer and activator of transcription 3 (STAT3) is a critical factor in the formation of tumor and tumor-related inflammation induced by chronic inflammation (34) due to its ability to mediate extracellular signals of inflammatory mediators and to regulate proliferation, invasion, angiogenesis, metastasis of cancer, and immunity. NF- $\kappa$ B and STAT3 are usually activated in the inflammatory process, which accelerates deterioration of tumors. Specifically, NF- $\kappa$ B promotes the proliferation of B lymphocytes and thymocytes, while STAT3

activates T lymphocyte proliferation, thus inducing cell apoptosis (35). Studies have also shown that tumor metastasis is promoted by the interaction between tumor cells and the inflammatory microenvironment (6). Therefore, targeting inflammatory pathways has been considered an effective intervention of malignant tumors in the past decades.

### ANTI-INFLAMMATORY AND ANTI-TUMOR INGREDIENTS OF TCM

A wide range of biologically active compounds have been extracted from TCM and their pharmacological activities have been investigated. Several main classes such as saponins, flavonoids, alkaloids, polysaccharides, polyphenols, phenylpropanoids, and quinones, have been reported to inhibit inflammation, activate inflammatory immune response, and/or inhibit cancer cell and tumor growth. In light of the link between inflammation and cancer, the inflammatory TME, and inflammation-induced tumor resistance to therapies, the ingredients of TCM that only demonstrate anti-inflammatory effects can also be applied to modulate the TME and enhance other cancer therapeutic modalities such as chemotherapy and immunotherapy.



**Figure 1.** Inflammation and tumor. Inflammation and tumor interaction via exogenous and endogenous pathways that lead to tumorigenesis by inducing the expression of pro-inflammatory molecules and promoting the formation of an inflammatory tumor microenvironment.

Furthermore, some components from TCM possess multitargeting activities and thus exhibit both anti-inflammatory and anti-cancer effects. Therefore, in the following sections, we present the ingredients of TCM with anti-inflammatory and anti-cancer properties side-by-side, together with their underlying mechanisms reported in literature. Their names, main sources, formulas, and chemical structures are presented in Table 1, while their anti-inflammatory and/or anti-cancer mechanisms are summarized in Table 2.

### Saponins

Saponins are compounds of saponin and sugar, uronic acid or other organic acids, which are widely found in plants. They are mainly divided into steroid and triterpenoid subtypes.

Astragaloside is the main component of *Astragalus membranaceus* that belongs to the Leguminosae family. Studies have found that astragaloside IV significantly decrease the generation of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 in RAW264.7 cells, which is induced by lipopolysaccharide (LPS), and increases the release of IL-10 (36). In addition, astragaloside IV increases the expression of NF- $\kappa$ B protein in a dose-dependent manner and inhibited the upregulation of p-Akt levels by LPS. Thus, astragaloside IV can inhibit inflammatory responses by regulating the expression of pro-inflammatory factors and anti-inflammatory factors in the Akt-NF- $\kappa$ B pathway (31). Astragaloside was also found to induce apoptosis in glioblastoma cell line SHG44 by activating the p53 signaling pathway and Bcl-2 family-mediated cytochrome C pathway (37). Astragaloside significantly inhibited growth of liver cancer H22 cells and sarcoma S180 cells transplanted into healthy mic, but had no significant effect on proliferation of the human hepatocellular carcinoma cell line HepG2, the human colon cancer cell line HCT11, and the human lung adenocarcinoma epithelial cell line A549 (38). Furthermore, total *Astragalus* saponins was reported to down-regulate mTOR expression, inhibit NF- $\kappa$ B expression, and cause exogenous apoptosis in HT-29 cells by influencing the PI3K/Akt signal pathway (39).

Total saponins of *Panax ginseng* (TSPG) are the main active ingredients of *Panax* plants of the family Araliaceae. TSPG was found to improve the release of inflammatory mediators such as NOS, reduce the expression of TNF- $\alpha$  and IL-1 $\beta$ , promote the translocation of NF- $\kappa$ B from the cytoplasm to the nucleus, downregulate

mitogen-activated protein kinase (MAPK) and Akt, and inhibit LPS-mediated inflammation in RAW264.7 cells (40). TSPG also inhibits proliferation of tumor cells in the G2/M phase and induces apoptosis by influencing cell cycle-related protein (cyclin) and cyclin kinases (CDK1, CDK2, etc.) in human cervical cancer (HeLa) cells (41).

*Panax notoginseng* saponins (PNS) exhibits dose-dependent inhibitory effect on the proliferation of gastric cancer cells (MKN-8) (42), and suppresses HeLa cells by inhibiting the assembly of translation initiation complexes (43).

### Flavonoids

Flavonoids, including baicalin and glycyrrhizin, are common active ingredients in TCM. They have been shown to exhibit antioxidant, anti-inflammatory, antimicrobial, and anticancer activities.

Baicalin can alleviate ulcerative colitis by inhibiting activation of the NF- $\kappa$ B pathway and down-regulating expression of pro-inflammatory cytokines (44,45). Baicalin can modulate P-STAT4/STAT4 and P-STAT6/STAT6 ratios and the expression of related factors *in vitro* to curb inflammatory reactions (46). Moreover, baicalin can suppress proliferation and migration of A431 skin squamous cancer cells (47), and inhibit cell proliferation, migration and invasion of LTEP-A2 lung adenocarcinoma cells by down-regulating MMP-2 and MMP-9 expression (48).

Glycyrrhizin exhibits protective effect against LPS-induced acute lung injury in mice by reducing the intracellular concentration of TNF- $\alpha$  and IL-1 $\beta$ , and inhibiting the expression of cyclooxygenase 2 (COX-2) and inducible nitric oxide synthase (iNOS) (49). Glycyrrhizin also has an ameliorative effect on myocarditis caused by Cocksackievirus B3 via inhibiting the expression of TNF- $\alpha$ , IL-6 and IL-1 $\beta$  (50). Besides, glycyrrhizin can suppress the proliferation of prostate cancer cells (51). Moreover, glycyrrhizin inhibits the development of colon precancerous lesion by inhibiting the activation of extracellular signal-regulated protein kinases (ERKs) in endothelial cells, the expression of vascular endothelial growth factor (VEGF) and angiogenesis (52).

### Quinones

Emodin and aloe-emodin are anthraquinones existing in rhubarb in large quantity. Recently they have been found to exert important effects against cancer (53-57). Emodin inhibits

proliferation and promotes apoptosis in human A549 lung adenocarcinoma epithelial cells by inhibiting VEGF expression and promoting TNF- $\alpha$  expression (53). It has also been shown to inhibit the metastasis of pancreatic cancer *in vivo* by down-regulating NF- $\kappa$ B and MMP-9 expression (54). Emodin also blocks cell cycle in the G0/G1 phase and inhibits proliferation of K562 cells by reducing Bcl-2 and Bax expression. Furthermore, it has been shown to inhibit the growth of transplanted tumor in nude mice by activating caspase-related signal transduction pathways (55). Emodin and aloë-emodin have been found to suppress the proliferation of breast cancer cells by targeting ER $\alpha$  protein stability (56). In addition, Emodin inhibits the growth of breast cancer by modulating the phenotype of tumor-associated macrophages (57).

### Phenylpropanoids

Osthole, a principle active ingredient from *Cnidium monnieri* (L.) Cusson, has been reported to exhibit multitarget pharmacological activities (58-61). It shows both anti-inflammatory and anti-tumor effects in HepG2 cells via inhibiting the NF- $\kappa$ B and MAPK signaling pathways and the production of inflammatory cytokines (59). Osthole can inhibit a variety of human malignant tumor cell lines, such as gastric cancer cell lines MKN-45 and BGC-823, lung adenocarcinoma cancer epithelial cell line A549, breast cancer cell line MCF-7 and colon cancer cell line LOVO (60). Besides, high concentration of osthole can inhibit the TGF- $\beta$ -dependent invasion and metastasis of human liver cancer cell HepG2 by down-regulating the level of MMP-9 and vimentin in cells (61).

Psoralen is one of the active ingredients in TCM *P. corylifolia* L., or Bu Gu Zhi. It can alter gene expression in human breast cancer cell line MCF-7, and is related to cell apoptosis, cell cycle regulation, nucleic acid translation, translation factor activity, nucleotide transferase activity and vasoconstriction (62). Moreover, it can suppress the proliferation of HepG2 cell by blocking the cell cycle in the G2/M phase (63).

### Alkaloids

Matrine, an alkaloid, exhibits anti-inflammatory effect on mice with LPS-induced intestinal inflammation *via* the release of the inflammatory mediator NO and the expression of cytokines TNF- $\alpha$  and IL-6 (64, 65). It can regulate the balance of Th1 and Th2 by reducing the expression of suppressor of cytokine signaling 3

(SOCS-3) (66). Matrine, *via* regulating the expression of intracellular Bid, Bcl-2 and Bax proteins, induces apoptosis in human hepatocellular carcinoma cell line HepG2 by mitochondrial signal transduction pathways (67). Besides, it can inhibit the proliferation of HeLa cells by upregulating the protein and mRNA levels of protein tyrosine phosphatase 2 (SHP-2) and SOCS-3, and negatively regulating the JAK-STAT signal pathway (68). Moreover, matrine promotes apoptosis of MCF-7 cell by reducing mitochondrial transmembrane potential (69). Matrine, at low concentrations, has also been found to induce T lymphocytes to secrete IL-2 and IFN - $\gamma$  which has bi-directional effects on the proliferation of human peripheral blood T lymphocytes (70).

### Polysaccharides

*Lycium barbarum* polysaccharide (LBP), an ingredient from wolfberry (Goji), can not only kill tumor cells, but also exert biological effects on the intermediate host. Acting on immune cells *via* multiple pathways, LBP induces the secretion of antibody and improves the organism's immune surveillance system, thereby inhibiting and killing tumor cells (71). Through down-regulating serum TNF- $\alpha$  levels in mice with liver cancer H22 and increasing the content of IL-2 and INF- $\gamma$ , LBP can increase the activity of natural killer cells, enhance the Th1/Th2 ratio, improve organism's immune system and then suppress tumor growth (72, 73). LBP can inhibit the growth of human liver cancer cell line HCCLM3 by promoting IL-2 production and reducing the expression of VEGF (74). LBP has not shown obvious effect on the proliferation of T cells, but it can promote the maturation of dendritic cells and enhance the proliferation of effector T cells, which results in tumor suppression (69).

### Polyphenols

Curcumin, a major component of turmeric, is an extensively studied polyphenol. It has a variety of activities including anti-inflammation, antioxidation, antitumor, anti-liver fibrosis and anti-infection functions (11, 76-79). Curcumin carries out its anti-inflammatory role by suppressing inflammatory mediators such as cyclooxygenase (COX-1, COX-2), lipoxidase (LOX), TNF- $\alpha$ , interferon  $\gamma$  (IFN - $\gamma$ ), iNOS, NF- $\kappa$ B and activator protein 1 (AP-1) (80-82).

Curcumin exhibits antitumor properties by regulating cell cycle, inducing apoptosis, inhibiting proliferation and metastasis of cancer

cells, and reducing the synthesis of inflammatory factors (78, 79). Numerous mechanisms and pathways have been identified for the antitumor activities of curcumin (70-84), for which a comprehensive review was published by Ravindran et al. in 2009 (76). In addition, recent research findings indicate that curcumin inhibits proliferation and promotes apoptosis of human colon cancer cells (LoVo and SW620) by upregulating the expression of p53, Bax and Caspase-3, and down-regulating the expression of Bcl-2 and c-myc (83, 84). It also inhibits the proliferation of SW1990 pancreatic cancer cells by suppressing STAT3 activation (85). Curcumin suppresses the proliferation of HepG2 liver cancer cells by reducing the level of NF-Bp65 mRNA,

the levels of mRNA and protein of downstream gene hTERT, and the activity of NF-κB and telomerase (86). Curcumin inhibits the growth of breast cancer cell line MCF-7 by regulating the mRNA levels of Bcl-2 and Bax, and decreases the invasiveness of cancer cells by down-regulating VEGF-C at both mRNA and protein levels (87, 88). In addition, curcumin has been found to block the activation of the NF-κB signaling pathway, inhibit the expression of neutrophil gelatinase-associated lipocalin, through the TGF-β/Smad and TGF-β/ERK signaling pathways, and downregulate TGF-β1-induced expression and the activity of MMP-9, thus inhibiting the invasion of MDA-MB-231 breast cancer cells (89, 90).

**Table 1.** Anti-inflammatory and Anti-tumor Ingredients of TCM

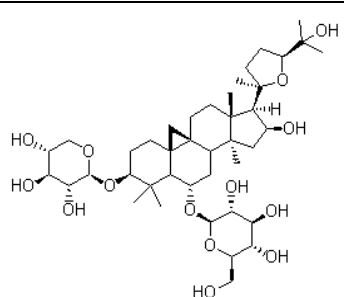
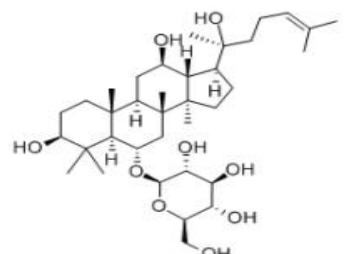
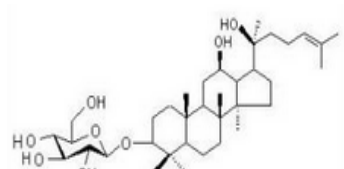
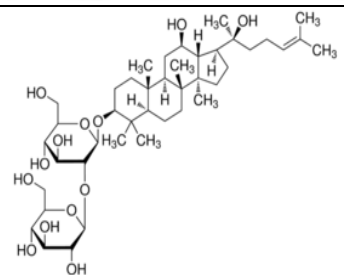
Active ingredient	Main Source	Formula	Structure	Reference
Astragaloside IV	Astragalusmembranaceus	C <sub>41</sub> H <sub>68</sub> O <sub>14</sub>		(36-39)
Ginsenosides Rh1	Panax ginseng	C <sub>36</sub> H <sub>62</sub> O <sub>9</sub>		(40-43)
GinsenosidesRh2	Panaxginseng	C <sub>36</sub> H <sub>62</sub> O <sub>8</sub>		(40-43)
GinsenosidesRg3	Panax ginseng	C <sub>47</sub> H <sub>72</sub> O <sub>13</sub>		(36-43)

Table 1. Continued.

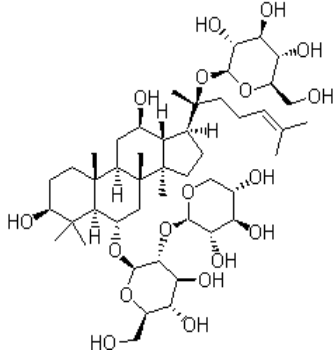
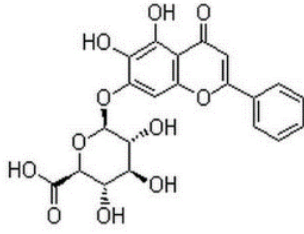
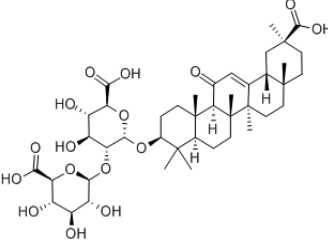
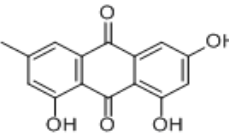
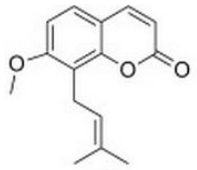
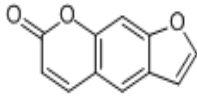
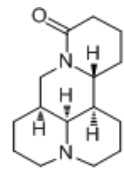
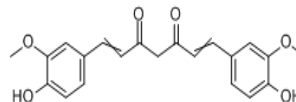
Notoginsenoside R1	Panaxnotoginseng	$C_{47}H_{80}O_{18}$		(36-43)
Baicalin	Scutellariabaicalensis	$C_{21}H_{18}O_{11}$		(44-48)
Glycyrrhizin	Glycyrrhiza	$C_{42}H_{62}O_{16}$		(49-52)
Emodin	rhubarb	$C_{15}H_{10}O_5$		(53-55)
Osthole	Cnidium	$C_{15}H_{16}O_3$		(59-61)
Psoralen	Psoraleacorylifolia Linn.	$C_{11}H_6O_3$		(62-63)
Matrine	Sophoraflavescens	$C_{15}H_{24}N_2O$		(64-70)

Table 1. Continued.

LyciumbarbarumP	Lyciumbarbarum	$(C_6H_{10}O_5)_n-(C_6H_{12}O_5)_n-(C_5H_{10}O_5)_n$	(71-75)
Curcumin	Polygonumcuspidatum, Rhubarb	$C_{21}H_{20}O_6$	(77-90)

**Table 2.** Summary of Possible Anti-inflammatory and Anticancer Mechanisms of Ingredients of TCM

Class	Known active ingredient	Anti-inflammatory effect	Anticancer effect	Reference
Saponins	Astragaloside IV	Decreases TNF- $\alpha$ , IL-1 $\beta$ , and IL-6; promotes release of IL-10; increases NF- $\kappa$ B expression, downregulates p-Akt	Induces apoptosis; upregulates p53, Bax; downregulates Bcl-2, mTOR; inhibits NF- $\kappa$ B	(36-39)
	Total saponins of Panax ginseng (TSPG)	Modulate NO/NOS; decrease TNF- $\alpha$ and IL-1 $\beta$ ; increase NF- $\kappa$ B expression; downregulate MAPK and Akt	Induce cell-cycle arrest in G1 and G2/M phases; induce apoptosis; decrease cyclin and CDK4	(40,41)
	Panax notoginseng saponins (PNS)		Induce cell-cycle arrest in G1 phases; induce apoptosis; upregulate death receptor-5 expression; down-regulate S6K1, 4E-PB1, mTOR	(42,43)
Flavonoids	Baicalin	Modulates P-NF- $\kappa$ B/NF- $\kappa$ B, P-STAT4/STAT4 and P-STAT6/STAT6	Inhibits cofilin-1-siRNA; inhibits cancer cell growth and migration; down-regulates MMP-2/9 expression	(44-48)
	Glycyrrhizin	Decreases TNF- $\alpha$ , IL-1 $\beta$ ; inhibits COX-2 and iNOS	suppresses proliferation; inhibits ERKs, and VEGF	(49-52)
Quinones	Emodin		Inhibits VEGF and TNF- $\alpha$ ; suppresses proliferation; induces apoptosis; downregulates NF- $\kappa$ B and MMP-9 expression; blocks cell-cycle in the G0/G1 phase; down-regulates Bax and Bcl-2; induces cytosolic ER $\alpha$ degradation	(53-57)

Table 2. Continued

<b>Phenylpropanoids</b>	Osthole	Inhibit NF- $\kappa$ B and MAPK signaling pathways	Inhibits NF- $\kappa$ B and MAPK signaling pathways; suppresses proliferation; down-regulates MMP-2/9 and vimentin expression; inhibits invasion and metastasis of cancer cells; prolongs survival of tumor-bearing mice	(59-61)
	Psoralen		induces cell-cycle arrest in G2/M phases; down-regulates CYP3A4; suppresses proliferation; induces apoptosis	(62-63)
<b>Alkaloids</b>	Matrine	decreases NO; increases ADMA and PRMT1 expression;	up-regulates TNF- $\alpha$ and IL-6; modulates Th1/Th2; induces cell-cycle arrest in G0/ G1 phase; down-regulates Bid, Bcl-2; up-regulates Bax; inhibits proliferation; down-regulates JAK-STAT; reduces mitochondrial membrane potential	(64-70)
<b>Polysaccharides</b>	Lycium barbarum polysaccharide (LBP)		Upregulates CD86, CD11a and IL-12P40; increases killing capabilities; modulates Th1/Th2; up-regulates IL-2 and INF- $\gamma$ ; down-regulates TNF- $\alpha$ ; inhibits tumor growth	(71-75)
<b>Polyphenols</b>	Curcumin	Suppresses COX-1, COX-2, LOX, TNF- $\alpha$ , IFN - $\gamma$ , iNOS, NF- $\kappa$ B and AP-1	Regulates cell-cycle; induces apoptosis; inhibits proliferation and metastasis; up-regulates p53, Bax and Caspase-3; down-regulates Bcl-2 and c-myc; suppresses STAT3 activation; reduces NF-Bp65 mRNA and hTERT gene expression; reduces telomerase activity; up-regulates VEGF-C; inhibits neutrophil	(76-90)



Table 2. Continued

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gelatinase-associated  
lipocalin, TGF- $\beta$ 1-induced  
MMP-9 expression; inhibits  
tumor invasion

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## SUMMARY AND OUTLOOK

The relationship between inflammation and cancer is a complex matter involving many types of cells and numerous signaling pathways (1-10). In the process of neoplasia, inflammatory cells promote the growth of tumor cells, genetic mutations, and angiogenesis. Within the TME, the growth, metastasis and differentiation of tumor cells are regulated by immune and inflammatory cells, and various chemokines and cytokines. Although many ingredients of TCM have exhibited activities in suppressing inflammation, preventing tumorigenesis, and controlling tumor growth, it is still unclear what the target inflammatory factors are and when the drugs and how much should be administered to control inflammation and strengthen immune surveillance. Hence, it is critical to gain thorough understanding of the underlying mechanisms of pharmacological effects of the active ingredients of TCM and their roles in the complex networks of inflammatory and immune response. It is also important to rigorously characterize the pharmacokinetics and biopharmaceutics of the active compounds of TCM and their interactions with other therapeutic agents (e.g. anti-cancer drugs) prior to pursuit of clinical trials to avoid unexpected bioavailability and toxicity issues (21,22).

So far, research on the anti-inflammatory and anti-tumor functions of TCM compounds has been limited to individual chemical constituents. However, clinically used TCM consists of multiple active ingredients, which may generate synergistic effects. Thus more research should be conducted to examine whether and how synergistic, additive and antagonistic effects of multiple components in a TCM contribute to the anti-inflammatory and anti-tumor functions. Up to date, the anti-inflammatory and anti-tumor effects of the same active ingredients of TCM are normally studied separately using different research models. Owing to the connections between pro-inflammatory and pro-tumor factors, it is desirable to investigate the anti-inflammatory and anti-tumor effects of TCM compounds together using integrated models. To accomplish this challenging task, advancement of

experimental methodology and increased efforts are urgently needed.

## ACKNOWLEDGEMENTS

This study was financially supported by the National Natural Science Foundation of China (81273707, 81173215); the Ministry of Education in the New Century Excellent Talents (NECT-12-0677); the Natural Science Foundation of Guangdong (S2013010012880); the Science and Technology Program of Guangzhou (2014J4500005); the Science Program of the Department of Education of Guangdong (2013KJCX0021); and the Science and Technology Program of Guangdong (2015A050502027). The Natural Sciences and Engineering Research Council of Canada is also acknowledged for the Discovery grant to XYW (RGPIN 170460-13).

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