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REVIEW

Research progress on synergistic anti-tumor mechanisms of compounds in Traditional Chinese Medicine

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Abstract

The curative effects of Chinese herbal compounds result from the coordination of numerous natural compounds. We aimed to review the mechanism of action of Traditional Chinese Medicine (TCM) compounds (TCMC), explore the rationality of formulation theory and synergistic effects in TCM compounds, and analyze the effectiveness of drug compatibility of TCMC in molecular biology. This literature review covers the mechanisms of the anti-tumor effects of compounds, and their synergistic antitumor mechanisms. We aim to provide reference for the effective development and use of natural resources and the organic combination of TCM and modern medicine using molecular biology.

Key words: Compounds; Traditional medicine, Chinese; Molecular biology; Monomer

INTRODUCTION

Traditional Chinese Medicine (TCM) treatment for tumors uses multiple components to target multiple sites and optimal efficacy. TCM combines medicines according to their natural odor, meridian tropism, and relationship of monarch, minister, assistant, and guide herbs. The combination of herbs has a network adjustment effect that is not present in Western Medicine. The modernization of TCM focuses on the study of active ingredients in Chinese medicines. This has led to the discovery of a variety of compounds, including artemisinin and tanshinone, which are effectively applied in clinic. The effectiveness of TCM does not lie in one or a few herbs, but in the entire prescription. The toxicity of some Chinese medicine compounds can be abated or gradually offset with extra herbs, but the overall efficacy is strengthened.[1] In this review, we summarized the mechanisms of the anti-tumor effects of effective compounds from TCM, and their synergistic antitumor mechanisms.

RESEARCH PROGRESS ON MOLECULAR MECHANISMS OF ANTI-TUMOR EFFECTS OF TCM COMPOUNDS

The curative effects of TCM compounds result from the coordination of natural compounds. For example, Zhou's Kejinyan compound is clinically effective for lung cancer. Anti-lung cancer recipes are composed of four types of functional drugs and aim to clear phlegm, dispel turbidity, promote the blood flow, remove stasis, regulate *Qi*, descend adverse flow of *Qi*, and tonify *Qi*

and nourish *Yin*.[2] By screening the prescription with high throughput screening, we get more than 20 compounds which have cytotoxic effects on non-small cell lung cancer, including quercetin, isoliquiritigenin, catechin compounds, ophiopogonin, ginsenosides, and bibenzyl compounds.

Quercetin cytostatic and pro-apoptotic effect on tumor cells

Quercetin and its derivatives are flavonoids found in plants, and are present in flowers, leaf, and fruit. They have many pharmacological effects including as an antioxidant, anti-inflammatory, hypotensive, and anti-coagulant. They also have cancer, aging, mutagenic, and atherosclerosis preventive activities.[3]

Jin *et al* [4] found that quercetin had an obvious inhibitory effect on the proliferation of A549 human lung adenocarcinoma cells and transplanted mouse Lewis's lung carcinoma cells. According to immunohistochemistry, quercetin could obviously lower proliferating cell nucleus antigen (PCNA) expression levels. By inhibiting the expression of PCNA, quercetin could reduce the activity of DNA polymerase D, and inhibit the synthesis of DNA in tumor cells. They also found that quercetin induced apoptosis of mouse melanoma Cloudman S91 cells in a dose-dependent manner.[5] The mechanism was via inhibition of the expression of gene protein p53 and BC-l2. This blocked the cell cycle progression from G_1 to S phase, and caused the cells in G_1 to accumulate, which lowered the PCNA expression level. Lower PCNA inhibited DNA synthesis in the S phase, and inhibited the proliferation of tumor cells.

In addition, Cipka *et al* [6] reported that quercetin could strengthen the apoptosis effect of cisplatin on human leukemia HL-60 and rat leukemia L1210 cells after joint administration.

Cytostatic and pro-apoptotic effects of isoliquiritigenin (ISL) on tumor cells

ISL is an isoflavonoid found in licorice, Guangguogancao (*Radix Glycyrrhizae Glabrae*), Zhangguogancao (*Radix Glycyrrhizae Inflatae*) dry root and rhizome, Huangqi (*Radix Astragali Mongolici*) root,[7] and Dahuangjing (*Rhizoma Polygonati Kingiani*) root.[8] It has antitumor, anti-oxidative, and anti-inflammatory effects. It also can expand the arteries and protect the heart and brain.[9]

Kanazawa *et al* [10] investigated the influence of ISL on the gene expression of cell proliferation, cell cycle control, and cell cycle regulation. They also studied the antitumor activity of ISL *in vitro* on prostatic cancer, using the prostate cancer cell lines DU145 and LNCaP. They found that ISL had significant dose- and time-inhibitory effects on prostatic cancer cell strains. Fluorescence activated cell-sorting analysis showed that ISL induced cell cycle block in the S and G_2/M phases, and enhanced the expression of GADD153 protein mRNA.

Hsu *et al* [11,12] found that ISL could inhibit the proliferation of human non-small cell lung cancer A549 cells. ISL could not only inhibit the proliferation of A549 cells, but also induce cell apoptosis and block cell cycle progression in G_1. ISL realized the anti-proliferative effect on lung cancer cells A549 through the p53 gene and the Fas/FasL cell apoptosis system. ISL could also inhibit the proliferation of human hepatocellular carcinoma cells. With an IC_{50} of 10.51 μg/mL, ISL can inhibit cell growth, and lead cells to programmed death by activating caspases. ISL can also inhibit the expressions of Bcl-xL and C-IAP1/2 proteins, and reduce the levels of NF-κB and its activities in the nucleus. Hsu *et al* also found that ISL could lead to a rise in p53 gene expression, and incrementally regulate p21/WAF1, Fas/APO-1 receptor, Fas ligand, Bax, and NOXA.

Cytostatic and pro-apoptotic effects of tea polyphenols and their catechins on tumor cells

Catechins are flavonoids and anthocyans of flavonoid glycosides. They are widely distributed in plants such as tealeaves, hawthorn, wild strawberries, cocoa fruit, and grape seeds. Catechins have biological activities such as anti-oxidative, anti-cancer, anti-inflammatory, anti-aging, and anti-mutation effects, and liver function improvement.[13]

Gupta *et al* [14] found that epigallocatechin gallate (EGCG) could induce cell cycle block and apoptosis of prostate cancer cells. It could increase the expression of WAF1/p21, KIP1/p21, INK4a/p16, and INK4c/p18 protein in a dose- and time-dependent manner, lower the expressions of cyclin D1, cyclin E, Cdk2, Cdk4, and Cdk, except for cyclin D2. It could also increase the combination of cyclin E, WAF1/p21, and KIP1/p21, decrease the combination of cyclin E and Cdk2, and inhibit the adjustment of cyclin Cdk complexes in the G_0/G_1 phase.

Sun *et al* [15] investigated the influence and mechanism of EGCG on lung cancer cell proliferation. The results showed that EGCG could significantly inhibit the proliferation of A549 cells. After administration of 60 mg/L EGCG, Hoechst staining showed obvious chromatin condensation, and dense or fragmental hyperchromatic cell apoptosis. The apoptotic rate was much higher than that of the control group. The survivin expression in many lung cancer tissues was the strongest apoptosis inhibiting factor found so far. Western blot showed that survivin protein expression in the treatment group was significantly inhibited, which indicated that EGCG suppressed the proliferation of lung cancer cells by inhibiting survivin expression and promoting lung cancer cell apoptosis.

Inhibition effect of ophiopogonin on tumor cells

Ophiopogonin is a steroid saponin, and mainly comes from the liliaceous plants Tumaidong (*Radix Liriopes Spicatae*), Shanmaidong (*Radix Liriopes Proliferae*), Duantingshanmaidong (*Radix Liriopes Musacarli*), and Kuoyeshanmaidong (*Radix Liriopes Platyphyllae*). Ophi-