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# Current insight on anti-tumor effect of natural products

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**Abstract:** Various clinical practices prove that traditional Chinese medicines, integrated traditionalChinese and western medicines make enormous contributions to tumor treatment as well as alleviation of chemotherapy side effect. Alkaloid, polysaccharide and saponin are examples of natural bioactive products that can impede the progression of tumors. Besides, researches on the widely-used tradition Chinese anti-tumor medicine formulas indicate that these agents can induce apoptosis of tumor cells. Therefore, there is an extensive perspective in natural bioactive materials as clinical tumor therapy. This review provides an overview of some natural products used as anti-tumor remedies and the molecular mechanisms they are involved in apoptosis induction, tumor angiogenesis and tumor metastasis.

**Key words:** Anti-tumor; natural product; apoptosis.

## Introduction

Cell apoptosis or programmed cell death indicates that cells receive various signals and cell death takes place subsequently under the gene regulation. It is an in-dispensable mechanism for the multicellular organisms to regulate the body metabolism and to maintain homeosta-sis. Failure of cell apoptosis may lead to diseases, mal-formationor even death. Studyshowedthere is a close relationship between the progression of cancer and the disorder of cell apoptosis.Apoptosis is involved in the initiation of cancer,it functions as negativeregulation. On the early stage of carcinoma, cells are susceptible to cell apoptosis, which exhibits the organism's self-defend ability. But the escaping of tumorous cells from the host immune system is a major problem that blocks the cancer treatment (1).Currently, many natural products have been used to isolate pharmacologically active ingredients (2). For example, curcumin, resveratrol, flavonoids, betulinic acid, ursolic acid, indole-methanol, evodiamine and green tea polyphenols are all candidates of plant-derived com-ponents that can suppress cell apoptosis through reducing Bcl-2, Bcl-XL,etc (3). Multidrug resistance is another major problem for effective cancer chemotherapy, and a majority of the cases are caused by the overexpression of P-glycoprotein or related ABC transporters (4,5). Some of the natural compounds, such as curcumin, resveratrol and flavonoids, have been proved to modulate multidrug resis-tance in cancer (6-8). Different from synthetic anti-tumor reagents, naturally isolated compounds requires deeper understanding of the molecular mechanismthey act on to reverse or prevent tumor development (9).

## Natural products and apoptosis-related signaling mo-lecules

Resveratrol can induce cell apoptosis in the way of blocking cell cycle progression at the G1 phase or the SG2 transition and reducing the amount of several types of cell products including the protein made in the D1 phase of cell-cycle, CDKs-4, Bcl-2 and Bcl-XL.Resveratrol has also been proved to act as the stimulator of p53-dependent p21 gene activation and the cell-cycle arrest due to the shortage of surviving (10). There are various antibodies and proteins, including p53 pathway, mitochondria-mediated pathway, death receptor pathway, caspases and some inducers, inhibitors, and detection kits, all of which can act as apoptosis signals.

Catechin is another potent pharmaceutical agent which, interestingly, exerts its growth-inhibitive effects on tumor cells exclusively without harm on normal cells (11). Emodin can selectively suppress IL-6-induced JAK2/STAT3 pathway in a variety of cancers, which makes it possible to trigger the apoptosis of myeloma cells (12). Curcumin has the apoptosis inductive ability onleucocythemia, malignant melanoma and mamma-ry carcinoma cells, etc. The mechanism of curcumin also involves stimulating Fas receptor pathways and inhibiting the expression of Bcl-2 and Bcl-XL (13,14). When indu-cing the cell apoptosis of epidermal keratinocyte, another product derived from plants called Silymarin can release cytochrome C and activate caspases. In the K562 cells, it inhibitsAkt-pathways, leading to caspases activation and the apoptosis progression (15).

## Natural products and tumor suppressor gene p53

Apoptotic protease is the executive factor for the cells' death and can be activated by various chemicals origina-ting from a plants source. Crcumin activates caspases-7 and caspases-9 when inducing the apoptosis of lymphoma cells and multiple myeloma. In human colorectal cancer cell HCT116 and gastric cancer cell KATO-III, curcu-min acts as the stimulator to activate apoptosis-related Fassignaling transduction pathway as well as apoptosis protease-8 and -3. Another apoptosisinducing way by

curcumin takes place in mitochondria, which involves the release of cytochrome C and the activation of apop-tosis protease-8 and -3. Another agent, resveratrol, exhi-bits extensive activity in inducing cell apoptosis for acute lymphoblastic leukemia (ALL). In the human malignant B cells, the principle mechanism of resveratrol is to induce the cell apoptosis by activating apoptosis protease-3 and p38 protein kinase pathways. Another mode of resvera-trol-induced cell apoptosis follows the paradigm of acti-vating apoptotic protease-2 via a special mechanism in mitochondria (10,16,17). Activated apoptotic protease-2 triggers the conformational change in the Bax/Bak with the release process of mitochondria cytochrome C, apop-tosis-inducing factor (AIF) and endonuclease G.

Tumor suppressor gene p53 and its expression product act as a key regulator to various cell activities including providing the cellular response to DNA damage, main-taining genome stability on the genetic level and regula-ting the cell-cycle and cell apoptosis on the cellular level. Over 50% of human tumor cells, flaws on gene p53 are detected, so it arouses a great interest on the remedy tar-geting this special gene.Curcumin, resveratrol, catechins, silymarin and Indole-3-Methanol are plant-deprived com-pounds working by potentiating or suppressing the acti-vity of gene p53.

Curcumin has a fairly complex mechanism among different tumor cells, including ovarian cancer cells, Hela tumor cells and human colonic carcinoma cell line. It can induce the cell growth arrest and cell apoptosis by nega-tively regulating the protein of egr-1,c-myc, Bcl-XL and p53. However, when inducing the apoptosis in the wild-type and mutant human melanoma p53 cell lines, no si-gnificant influence on the expression of gene p53 was ob-served. It can arrest the cell cycle of Immortalized Huma-nUmbilical Vein Endothelial Cells (HUVECs) by way of enhancing several kinds of thecyclin-dependent kinase in-hibitor including p21WAF1/CIP1, p27 and p53 (18,19).

Resveratrol has been proved to have efficacy on p53 as well. It exerts the apoptosis induction on the expres-sion of the wild-type gene p53 and tumor cells with gene p53 defect remain unharmed. Therefore the mechanism of action to induce cell apoptosis is to stimulate gene p53 activity by resveratrol. Drug NAG-1 (NSAIDS) activating gene is one of the members of transforming growth fac-tor-βand its expression is related to the activity of apopto-sis inducing and anti-tumor factors. Resveratrol enhances the expression of NAG-1 by potentiating the expression of p53 in human colon cancer cell lines. Resveratrol shows anti-proliferative effect on osteosarcoma via activated ERKs/p53 signaling pathways (18). Catechin has a potent efficacy on enhancing the expression of protein p53 and p21/WAF1 in human liver cancer cell line HepG2, which facilitates the cell cycle arrest (11). However, p53 doesn't show any impact ingenistein's inducing cell apoptosis, ar-resting cell cycle G2 and inhibiting proliferation (8).

**Targeting factors affecting angiogenesis and inhibition**

Angiogenesis plays a vital role in the cancer deve-lopment. During the process of angiogenesis, existing blood vesselsfirst get permeable and dilated, followed by the gradual degradation of the extracellular matrix. En-dothelial cells begin proliferating and migrating, after which support cells such as pericytes are finally recruited. Therefore, inhibiting the angiogenesis is of significant for the cancer treatment. Curcumin,resveratrol, catechin, ge-nistein, luteolin and capsaisinareare examples ofnatural products to potently regulate the angiogenesis.

Catechin suppresses the activity of oxidant-induced interleukin-8(IL-8). It can also inhibit the phosphoryla-tion of e-cadherin on epithelial cells, and the Akt activa-tion induced by vascular endothelial growth factor (11). Resveratrol shows potent efficacy against tumor-induced new blood vessels in organs (16,20). Curcumin, genistein and some compounds derived from green tea can interfere with the normal function of epithelial cells by inhibiting specific integration and signaling pathways (8).

**Targeting factors interfering with invasion and migra-tion**

Tumormetastases are the main cause for the deterio-ration or even death of the cancer patients. Tumor inva-sion and metastasis progression is extremely complicated. Challenge remains due to the lack of fundamental unders-tanding regarding the relationship between the natural bioactive products and the tumor invasion and metastases.

Curcumin are used to suppress the expression of membrane surface adhesion moleculesand induce the de-gradation of intercellular adhesion molecules (ICAMs) including β- catenin and E-cadherin (13). Curcumin in-hibits the cytokines promoting the growth of tumor cells such as tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1). Curcumin can also be used to decrease the acti-vity of matrix metalloproteinases-2 and -9 and degrades the extracellular matrix. Both curcumin and catechincan hamper the invasion of melanoma cells by suppressing matrix metaloproteinases (15). Fructooligosaccharide can prevent various kinds of chronic diseases and cancers by eliminating toxin from the body to reduce the burden on the liver (21).

Based on the model of postoperative Ductal Carcino-ma *in Situ*, genistein has been used to inhibit the tumor cell proliferation and increase the death rate of tumor cells in lungs, which potently suppress the tumor metastases (8,22). As for the resveratrol, theinhibiting action on the invasion of hepatocarcinoma cells is independent from its anti-proliferation action. On the other hand, in the hu-man K562 cell lines, it has an impact on inducing the ex-pression of cellular-matrix adhesion proteins andtensins, one of the tumor-inhibiting proteins. With the induction of tensin, resveratrol can regulate the regeneration of cel-lular-matrix adhesion proteins and suppress the invasion tensin-defective tumor cells. In incubated glioblastoma cells, resveratrol shows its efficacy against the expression of matrix metalloproteases-2 (MMP-2). It also reducesthe acidity of secreted protein that is rich in cysteines. Both actions are major factors of the extracellular matrix re-lated to tumor invasion (16).

**Conclusions**

Natural bioactive products are promising in cancer therapy but the concern is that their effects on inhibiting tumor cells' growth and inducing cell apoptosis are mainly based on *in vitro* experiments (22,23). The *in vivo* condi-tion is far more complicated and the unified theory remains unknown. For example,some of the natural products can

directly kill tumor cells; some will exhibit killing action only after the body metabolism; others can influence the immune system and endocrine system and then suppress cancer indirectly by hormone and cytokines. Hence, an in-creasing number of investigations*in vivo* with the modern pharmacological analysis method will bring a broader propective to the researchand exploitation of natural pro-ducts. Another challenge is the shortage of deep unders-tanding of the natural products' mechanism of suppressing cancer which includes natural products' initial factors and the relationship with cell-surface receptors. Further stu-dies are required to enhance the bioavailability of natural bioactive products and how they reduce the drug resis-tance in cancer chemotherapy (24,25).

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