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Research progress of curcumin in anti-tumor effect

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Abstract: *Curcumincumin is the main active component of the rhizoma Curcumincuma longa, a hydrophobic polyphenol with a wide range of biological and pharmacological activities. It can be used to treat tumors, diabetes, inflammation, neurodegenerative diseases, cardiovascular diseases, metabolic syndrome and liver diseases, etc. This article reviews the anti-tumor effects and mechanisms of Curcumincumin, such as targeted regulation of tumor cell cycle, inhibition of angiogenesis, and promotion of tumor cell apoptosis and other related signaling pathways and targets. It is hoped to provide some reference for the clinical research and application of Curcumincumin in anti-tumor in the future.*

Keywords: *Curcumin; Esophageal carcinoma; Anticancer properties; Research progress*

1. Introduction

Curcumincuma longa is a Curcumincuma genus of Zingiberaceae. It grows widely in southwest of China[1]. The earliest recorded medicine of Curcumincuma longa in our country's Tang Bencao (Materia Medica of the Tang Dynasty) was warm in nature, bitter and spicy in taste, and returned to the spleen and liver meridians. It was said that "the main heart knot accumulation, cystic disease, qi breaking blood, in addition to wind and heat, eliminate carbunction and swelling" [2]. Curcumin is an active compound extracted from the dried rhizome of Zingiberaceae plants such as Curcumincuma longa, Zedoary turmeric, and Curcumincuma vulgare [3]. The molecular formula of Curcumin was C21H20O6 and the molecular weight was 368.4 g/mol. The 2D and 3D structures of Curcumin were downloaded from Pubchem website. See Figure 1. Kuttan R et al. [4] first proposed that Curcumin could be used in anti-tumor therapy in 1985. More and more studies have confirmed that Curcumin plays an anti-tumor role by inducing tumor cell apoptosis, regulating tumor cell growth signal transduction pathway, inhibiting tumor angiogenesis and increasing the sensitivity of tumor cells to chemotherapy [5-7]. In addition to medicinal use, Curcuminoids are also used as food pigments and are one of the main ingredients of Curcuminry [8]. Compared with western medicine, it is cheap and safe, and has fewer adverse reactions. It has broad prospects in the treatment and prevention of tumor diseases [9].

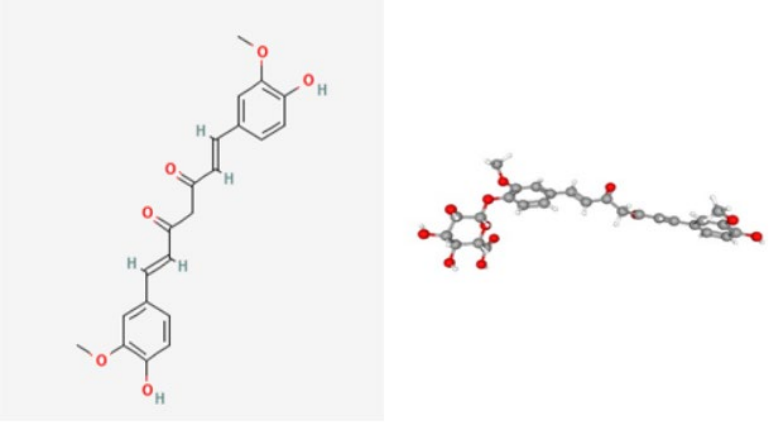

Figure 1: 2D structure of the Curcumin compound and 3D structure of the Curcumin compound

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According to the latest global cancer data in 2020 released by the International Agency for Research on Cancer (IARC) of the World Health Organization, the number of new cancer cases and cancer deaths in China ranks first in the world [10]. Tumor refers to the uncontrolled growth or even infinite abnormal proliferation of local tissues in the body under different carcinogenic conditions, which is the local manifestation of systemic diseases. Traditional Chinese medicine (TCM) is one of the important means of tumor treatment in China. Its main advantage lies in improving the internal environment of the body, especially in remodeling the tumor-related microenvironment [11]. Traditional Chinese medicine experts put forward that "when the positive qi is insufficient, the evil qi is behind", indicating that the basic pathogenesis of malignant tumors is a continuous struggle between "positive deficiency" and "evil poison" [12]. TCM improves the body's immune function and inhibits the proliferation and migration of cancer cells, thereby reducing the growth, metastasis and reCurcuminrence of tumor cells and preventing the ocCurcuminrence of tumors [13]. Through a large number of literature studies, it has been confirmed that Curcumin is particularly effective in the treatment of tumors, which is summarized as follows.

2. Curcumin and nasopharyngeal carcinoma

Nasopharyngeal carcinoma (NPC) is a malignant epithelial tumor originating from the nasopharynx, most of which is geographically located in Southeast Asia, while China is one of the countries with the highest incidence and mortality. Lin et al. [14] confirmed that Curcumin can significantly inhibit the growth of human poorly differentiated nasopharyngeal carcinoma cell line CNE-1, and S phase arrest prevents cells from entering the next proliferation cycle. By affecting the distribution of cell cycle, it affects the metabolism and function of cells, so as to achieve the purpose of inhibiting cell proliferation. Wang et al. [15] found that the high expression of PI3K and Akt phosphorylation levels in CNE-2Z cells were effectively inhibited after Curcumin intervention, suggesting that inhibition of endogenous PI3K/Akt pathway is one of the mechanisms of Curcumin anti-tumor. Tiam1 is a gene related to tumor invasion and metastasis. It can specifically activate the GTPase activity of Rho protein family, and its downstream effector is Rac1, an important member of Rho protein family. "Cellular endocytosis and membrane transport, cell migration, adhesion, invasion, apoptosis, and tumorigenesis." Chen et al. [16] confirmed that Tiam1 was highly expressed in nasopharyngeal carcinoma tissues by immunohistochemistry, and the expression of Tiam1 protein was determined by treating nasopharyngeal carcinoma cells with different concentrations of Curcumin. The results suggested that with the increase of Curcumin concentration, the expression of Tiam1 in nasopharyngeal carcinoma 5-8F cells decreased. The migration and invasion of cells were inhibited, further indicating that Curcumin may inhibit the invasion of NPC by inhibiting the expression of invasion related gene Tiam1.

3. Curcumin and lung cancer

Lung cancer is the second most common cancer in the world with a high mortality rate. The incidence of lung cancer is closely related to the maturity of the tobacco epidemic [10]. Jin et al. [17] found that Curcumin treatment of human lung adenocarcinoma cell line A549 could inhibit cell proliferation, induce cell apoptosis and increase caspase-3 activity. Further studies showed that Curcumin inhibited the proliferation and induced apoptosis of human non-small cell lung cancer cells by up-regulating miR-192-5p and inhibiting PI3K/Akt signaling pathway. Chen et al. [18] found that after the treatment of A549 cells with Curcumin, the inhibition of cell viability increased and the proportion of apoptotic cells increased gradually with the increase of the concentration, and the inhibition of lung cancer cells was achieved by reducing the Akt signaling pathway in lung cancer cells. Xu et al. [19] found that neutrophil elastase plays an important role in regulating lung tumor proliferation in the inflammatory microenvironment of A549 cells. Curcumin can inhibit tumor proliferation induced by neutrophil elastase. Curcumin can also inhibit the growth of cancer cells by up-regulating the expression levels of P53 and P21 genes in A549 cells, down-regulating the expression levels of PC-NA and IF4E genes, and initiating the P53/P21/PCNA/IF4E signaling pathway [20-21]. Li et al. [22] found that when A549 cells were treated with different concentrations of Curcumin for 24 h, the expression level of MMP-9 was significantly decreased and the level of TIMP-1 was significantly increased with the increase of concentration. Further studies showed that Curcumin inhibited the expression of phosphorylated ERK1/2 (p44/42) in a concentration-dependent manner. However, the expression of non-phosphorylated ERK1 did not change significantly, indicating that Curcumin promoted the apoptosis of A549 cells by inhibiting the phosphorylation of ERK1/2 signaling pathway.

ISSN 2618-1584 Vol. 5, Issue 8: 108-114, DOI: 10.25236/FMSR.2023.050815

4. Curcumin and gastric cancer

Gastric cancer is a highly malignant tumor, ranking fifth in morbidity and fourth in mortality in the world [10]. Early endoscopic radical resection can Curcumine more than 90% of gastric cancer, but chemotherapy and radiotherapy are not effective for advanced gastric cancer. It has been reported that Curcumin can inhibit the proliferation of gastric cancer cells by inducing apoptosis. In vitro, Curcumin can induce apoptosis of gastric cancer cells by promoting the disintegration of MMP, and MMP plays an important role in initiating the mitochondria-dependent apoptosis pathway [23]. Kruppel-like factor 4(KLF4) is a transcription factor that plays an important role in cell development and progression. Curcumin combined with KLF4 could block the cell cycle of BGC-823 cells in G1 phase. Western blot showed that the expression levels of p-PI3K and cyclinD1 were increased, and the expression of p-ERK was decreased. These results indicated that the combination of Curcumin and KLF4 could inhibit the proliferation of human BGC-823 cells by regulating PI3K/Akt and ERK/MAPK pathways [24]. Curcumin can inhibit the proliferation and induce apoptosis of gastric cancer cells by inducing cell cycle arrest in G2/ M phase, down-regulating the expression of glycolytic enzymes and effectively inhibiting the miR-21 /PTEN/Akt molecular pathway [25]. Curcumin induces apoptosis of gastric cancer cells in vitro and in vivo in conjunction with chemotherapy drugs such as 5-fluorouracil and oxaliplatin through Bcl/Bax-caspase8, 9-caspase3 pathway [26]. Yang et al. [27] conducted a clinical study on 56 patients with advanced gastric cancer, and the results showed that Curcumin adjuvant chemotherapy drugs could improve the therapeutic effect of patients with advanced gastric cancer, reduce the adverse reactions of chemotherapy, and improve the tolerance of patients compared with the chemotherapy group.

5. Curcumin and liver cancer

Liver cancer ranks fifth in the global incidence and is the third leading cause of cancer death. In China, the infection rate of hepatitis B virus is the most important risk factor, and reducing the exposure to alcohol and aflatoxin can reduce the incidence [10]. The expression of mirNA-29 and mirNA-30 family members is elevated in normal liver and breast cancer liver metastasis models, and multiple members of each miRNA family directly target and inhibit the insulin-like growth factor-1 (IGF-1) /IGF-1 receptor (IGF-1R) signaling axis, which is associated with reduced cancer progression and metastasis [28]. Chen Caiping et al. [29] found that the inhibition rate of hepatocellular carcinoma HepG2 cells was the best after 72 hours of culture, and Curcumin may regulate the biological process of hepatocellular carcinoma cells by increasing the expression of miRNA-29 and reducing the expression of vascular endothelial growth factor (VEGF). miRNA-21-5 promotes the growth, migration and invasion of hepatocellular carcinoma (HCC) cells by targeting downstream target genes, such as FASLG, suppressor of cytokine signaling 6(SOCS6) and Kruppel-like transcription factor 5(KLF5) [30]. Studies have shown that Curcumin can down-regulate the expression of miRNA-21, up-regulate the expression of TIMP3, and inhibit the transforming growth factor β1(TGF-β1)/recombinant SMAD family member 3(SMAD3) signaling pathway, thereby inhibiting the proliferation of HepG2 and HCC LM3 cells [31]. In addition, Curcumin can also reduce the expression of miRNA-21-5p and increase SOX6 expression to inhibit the proliferation, migration and invasion of HCC cells [32].

6. Curcumin and colorectal cancer

The incidence of colorectal cancer is the third in the world, and the mortality rate is the second due to its insidious early stage, easy reCurcuminrence and metastasis in the late stage [10]. Fang Li [33] et al. found that Curcumin could inhibit the expression of Cyclin D1 in human colon cancer HT-29 cells in a dose - and time-dependent manner. In addition, Curcumin inhibited the activation of activator protein-1 (AP-1) in colon cancer cells, resulting in the overexpression of miR-21 gene binding to the miR-21 promoter. Under the regulation of miR-21, colon cancer cell cycle was arrested in G2/M phase. Thereby inhibiting the abnormal and rapid proliferation of tumor cells .In the study of Curcumin-induced apoptosis of tumor cells, Curcumin can effectively disturb the balance of mitochondrial membrane potential, enhance the inhibition of Bcl-xL protein, and regulate cell apoptosis [34]. Luo Qiang [35] treated human colon cancer SW620 cells cultured in vitro with different concentrations of Curcumin for 24 h, and found that the proliferation ability of tumor cells was significantly inhibited in a dose-dependent manner. At the same time, SW620 cells were regulated by Bcl-2 signaling pathway and underwent apoptosis. Curcumin was applied to colon cancer SW480 cells cultured in vitro. RT-qP CR and Western blot experiments showed that Curcumin could regulate the apoptosis of colon cancer SW480 cells by recruiting Fas death receptor and activating downstream signals of death receptor pathway [36]. Zhang et

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al. [37] found that Curcumin significantly inhibited the proliferation of colon cancer SW620 cells and upregulated the expression of NKD2 in colorectal cancer cells and xenografts, leading to the down-regulation of key markers in Wnt signaling. In addition, Curcumin inhibited the progression of epithelial-mesenchymal transition (ETM) through the overexpression of E-cadherin and the down-regulation of vimentin.

7. Curcumin and gynecologic tumors

7.1. Ovarian cancer

Ovarian cancer is a common malignant tumor in the female reproductive system with high mortality and poor prognosis. SEO et al. [38] found that an abnormal increase in the expression level of muscle/endoplasmic reticulum calcium atpase (SERCA), which regulates Ca (2+) homeostasis, was observed in ovarian cancer. Curcumin induced apoptosis of ovarian cancer cells in a concentration - and time-dependent manner, and the solute Ca (2+) flux in ovarian cancer cells was significant (15μM). It was further confirmed that inhibition of SERCA activity by Curcumin could disrupt Ca (2+) homeostasis, thereby promoting apoptosis of ovarian cancer cells. Liu et al. [39] found that Curcumin significantly reduced cell viability and induced apoptotic cell death in human ovarian cancer cell lines SK-OV-3 and A2780, and induced protective autophagy in human ovarian cancer cells by inhibiting the AKT/mTOR/p70S6K pathway. WEIR et al. [40] found that Curcumin can inhibit the proliferation of cisplatin-resistant (CR) and sensitive (CS) human ovarian cancer cells, activate caspase-2 and PARP degradation to enhance p53 phosphorylation and apoptosis, thereby inducing G (3) /M phase cell cycle arrest in CR cells.

7.2. Cervical cancer

Cervical cancer is the fourth most commonly diagnosed cancer and the fourth leading cause of cancer death in women [10]. Cervical cancer and human papillomavirus (HPV) infection have a great correlation. Curcumin can significantly down-regulate the expression of HPV E6 mRNA in HeLa cells of cervical cancer, so as to play an anti-HPV effect, and promote the generation of reactive oxygen species (ROS) and damage DNA [41]. By inhibiting the activity of PI3K/Akt/mTOR, Curcumin can induce autophagy and inhibit the proliferation of cervical cancer SIHA cells, up-regulate the expression of tumor suppressor genes p53, p21 and p27, and secrete IFN-γ [42].

8. Curcumin and esophageal cancer

The incidence of esophageal cancer ranks the seventh in the world, and the overall mortality ranks the sixth [10]. China is a high-incidence area of esophageal cancer, and pickled vegetable consumption, smoking, alcohol consumption, low intake of fruits and vegetables are all its risk factors [43]. Li et al [44]. found that Curcumin inhibited the proliferation of esophageal cancer Ec109 cells by up-regulating the expression of PTEN, GSK3β and Caspase 3 and inhibiting the PI3K/Akt signaling pathway. Lin et al. [45] found that Curcumin inhibited the formation of Rac1-PI3K-Akt signaling complex related to lipid rafts in EC cells, and inhibited the invasion of EC cells induced by stromal cell-derived factor-1α (SDF-1α) through the localization of lipid rafts on the cell surface and the enhancement of matrix metalloproteinase-2 (MMP-2) promoter activity. Chen et al. [46] confirmed that after 48 hours of intervention with different concentrations of Curcumin, the cell cycle of esophageal cancer Eca-109 cells changed significantly, the proportion of cells in G0/G1 phase decreased significantly, and the proportion of cells in G2/M phase increased significantly. These results indicated that Curcumin could induce G2/M phase arrest, inhibit the proliferation and induce apoptosis of Eca-109 cells.

9. Curcumin and other tumors

Zhao et al. [47] found that Curcumin inhibited the growth of mouse prostate cancer xenografts in vivo and promoted the apoptosis of prostate LNCaP cells by inhibiting JNK pathway in vitro. Liu et al. [48] confirmed that Curcumin treatment of prostate cancer cell lines Du44 and 133RV145 inhibited the proliferation and invasion of cancer cells in vitro, as well as cell cycle arrest. Gong et al. [49] found that the viability of human renal cell adenocarcinoma ACHN cells was inhibited and the number of apoptosis increased after Curcumin treatment. The results in C57BL / 6 nude mice verified that the tumor size,

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weight and volume were also significantly inhibited after Curcumin treatment, and confirmed that the expression of AKT/mTOR protein in the treatment group was significantly reduced, while autophagy-related proteins were significantly increased. These results indicate that Curcumin plays a role in anti-renal cell carcinoma through AKT/mTOR pathway. Zhou et al. [50] found that Curcumin had stronger cytotoxic activity on acute myeloid leukemia (AML) cells, and flavin inhibited the phosphorylation of AKT, PRAS70, 6E-BP1, P27S2K, RAF-5 and p1 in AML cell lines (ML-4 and OCI-AML1) in a dose-dependent manner. Regulation of cell cycle D21 leads to cell cycle arrest and apoptosis in ML-5 and OCI-AML79 cells. Hu et al. [51] found that Curcumin showed anti-proliferation and colony formation inhibitory activities in the treatment of human breast cancer MCF-7 and MDA-MB-231 cell lines, and it also inhibited the migration of MDA-MB-231 cells. In addition, Curcumin downregulated the mRNA expression of Vimentin, Fibroniconin and β-catenin, and upregulated the mRNA expression level of E-cadherin, indicating that the inhibitory effect of Curcumin on breast cancer cells was closely related to epithelial-mesenchymal transition (EMT). Shi et al. [52] found that Curcumin can inhibit the cell proliferation of bladder cancer cells T24 and 5637, and reduce the migration and invasion ability of T24 and 5637 cells by regulating the expression of β-catenin and reversing EMT. BHARTI et al. [53] found that the transcription factor nuclear factor-kappaB (NF-kappaB) plays a central role in cell survival and proliferation of human multiple myeloma (MM), and that Curcumin could down-regulate the expression of NF-kappaB-regulated gene products, including IkappaBalpha, Bcl-2, and Bcl-2. Bcl-x (L) and cyclin D1. This resulted in the arrest of the G (1) /S phase of the MM cell cycle and effectively inhibited the proliferation of MM cells. Thus, it provides a molecular basis for the use of Curcumin in the treatment of MM patients.

10. Conclusion and Outlook

In summary, more and more studies have shown that the anti-tumor activity of Curcumin involves the regulation of a variety of cell signaling pathways, and acts on a variety of molecular targets, including transcription factors, cytokines, growth factors and their receptors, enzymes, inflammatory factors, and genes regulating cell proliferation and apoptosis. The above research results let us see the benefits of Curcumin in the treatment of animal and human tumors, but it has not yet entered the clinical anti-experiment. It is still necessary to develop Curcumin and its derivatives and new dosage forms to improve its absorption and metabolic characteristics, in order to find a more appropriate dose or dosage form, give precise anti-tumor treatment for specific tumors, and improve the efficacy. It has become a clinically effective tumor treatment drug.

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