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Research in the Study of the Anti-tumor Mechanism of Emodin

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Abstract

Emodin, as a natural and low-toxicity anticancer drug, has many functions, such as inhibiting of tumor cell growth and proliferation, influence of tumor cell cycle, induction of tumor cell apoptosis, inhibition of tumor cell metastasis, inhibition of angiogenesis, enhancement of chemotherapy sensitivity, etc. Taking "emodin", "tumor" and "mechanism of action" as the main keywords, this paper searched the databases of CNKI, VIP, Wanfang and PubMed from 2015-01-01 to 2021-12-31, reviewed various anti-tumor mechanisms and progress of emodin, providing reference for anti-tumor therapy.

Keywords

Emodin; Anti-tumor; Mechanism of action; Research progress; Review literature.

1. INTRODUCTION

Malignant tumor is seriously harmful to human life and health, and its mortality rate is second only to cardio-cerebrovascular diseases. Researchers are committed to finding effective drugs and treatments. In recent years, a number of studies and clinical trials have shown that traditional Chinese medicine can act on many aspects of tumor occurrence and development, has the advantages of high safety, low price and fewer adverse reactions, and has made considerable achievements in anti-tumor. Emodin is one of the most concerning traditional Chinese medicine, its anticancer mechanism has made great progress in recent years, and the specific mechanism will be described in the latter part. By collating the relevant literature in the past 6 years (2015-2021), this paper focuses on the mechanism of emodin on different tumor cells, which is of some significance for understanding the therapeutic effect of emodin on tumors. It not only provides a reference for emodin anti-cancer clinical research but also provides convenience for emodin follow-up research.

2. SOURCES AND PHARMACOLOGICAL EFFECTS OF EMODIN

The chemical name of emodin is 1,3,8-trihydroxy-6-methylanthraquinone, which is a natural anthraquinone derivative mainly derived from the rhizomes and roots of Rheum palmatum L., Polygonum multiflorumThunb., Polygonum cuspidatum Sieb. et Zucc. , is a phytoestrogen[1]. Modern pharmacological studies have shown that emodin can anti-inflammatory, antioxidation, diuresis, protect liver, relax blood vessels and promote gastrointestinal peristalsis, etc[2].It has been reported that emodin can regulate cell growth[3], regulate cell signal transduction[4], induce cell apoptosis[5], and inhibit cell invasion and metastasis[6]. And combined with other drugs to reverse drug resistance[7], enhance the efficacy of chemotherapy and other anti-tumor effects[8].

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3. STUDY ON THE ANTI-TUMOR MECHANISM OF EMODIN

3.1. Inhibit the growth and proliferation of tumor cells

Many tumor suppressor genes have aberrant methylation in pancreatic cancer, including CDKN1C, SPARC, P16, RASSF1A and ppENK. Hao Zhang et al.[3] have showed that emodin affects genome-wide expression through demethylation, especially reduces the methylation level of tumor suppressor genes P16, RASSF1A and ppENK, and inhibits the growth of pancreatic cancer cells. Ling Tang et al.[9] have shown that emodin inhibits the growth of non-small cell lung cancer (NSCLC) cells through PPAR- γ induction mediated by ERK and AMPK- α, and then inhibits Sp1. The aryl hydrocarbon receptor (AhR) is a ligand-binding transcription factor that regulates various biological processes. It has been found that many drugs used as AhR activators have certain anticancer activities. Recently, a virtual screening study by N. Zhang et al.[10] show that emodin is an effective AhR agonist in breast cancer chemotherapy, which can activate AhR, inhibit the proliferation of MCF-7 breast cancer cells, and promote cell apoptosis. Iwanowycz[11] show that emodin has an effect on breast cancer cells and macrophages, and can effectively block the tumor-promoting feedforward circuit between the two cells, thus inhibiting the growth and metastasis of breast cancer. In addition, the experimental team of K. Song[12] used gene chip analysis to find that emodin had a significant effect on the transforming growth factor TGF-β2 of ovarian cancer A2780 cells. It has been proved that emodin can directly promote the expression of Foxd3 in vitro, then activate MIR-199a, thus inhibiting the expression of TGF- β2 and decreacing the cell viability and colony formation of A2780 cells.

3.2. Affects tumor cell cycle

Wang et al [13] have found that the anti-proliferation effect of emodin is related to the decreased expression of cell cycle regulatory factors Cyclin D1 and Cyclin E1. In addition, it was found that there was a correlation between the down-regulation of these cell cycle regulatory factors by emodin and the up-regulation of caspase-3 cleavage in gynecological tumor cell lines[13]. The results showed that emodin could inhibit the proliferation of gynecological cancer cells and block the cell cycle by regulating cyclin. Deng's research team[14] found that emodin could activate the Notch signal pathway in PC3 prostate cancer cells and inhibit the proliferation of PC3 cells by inducing cell cycle arrest in G2/M phase and up-regulating the expression of Notch1. And M.Li et al.[15] showed that emodin can down-regulate cyclin A and B, up-regulate cyclin C and D, increase the number of cells in G1/G0 phase, reduce the number of cells in S phase and G2/M phase, and inhibit NSCLC cells by regulating the cell cycle.

3.3. Induce apoptosis of tumor cells

3.3.1 PI3K/AKT signal pathway

Phosphatidylinositol 3-kinase (PI3Ks) signal is involved in the regulation of many cellular functions, such as proliferation, differentiation, apoptosis and glucose transport. In recent years, it has been found that the signal pathway composed of IA type PI3K and its downstream protein kinase B (PKB or AKT) is closely related to the occurrence and development of human tumors. This pathway regulates the proliferation and survival of tumor cells, and its abnormal activity can not only lead to malignant transformation, but is also related to tumor cell migration, adhesion, tumor angiogenesis and extracellular matrix degradation.

Dai et al.[4] found that emodin can inhibit the growth, adhesion and migration of human colorectal cancer cells by inhibiting the VEGFR2/PI3K/AKT signaling pathway, which can be used as a potential therapeutic candidate. In addition, Jiang et al.[16] also found that emodin significantly inhibited the phosphorylation of AKT, enhanced the phosphorylation of MAPK pathway, upregulated the production of reactive oxygen species (ROS) in KLE cells, and

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promoted apoptosis of human endometrial cancer cells by regulating MAPK and PI3K/AKT pathways. Wang's research[17] team found that emodin effectively induced renal cancer cell necrosis by activating JNK signal pathway and had no significant cytotoxic effect on non-cancerous renal tubular epithelial cells. Further studies have shown that emodin can inhibit glycolysis by enhancing the down-regulation of reactive oxygen species (ROS) to the inactivation of glut1-mediated PI3K/AKT signaling pathway.

3.3.2 NF- κB signal pathway

NF- κB is widely used as a gene regulator to control cell proliferation and cell survival in eukaryotic cells. Trib3 was initially identified as a pseudokinase that inhibits mitosis in Drosophila embryos and germ cells. Further studies found that Trib3 is expressed in many human cell types, suggesting that Trib3 plays an important regulatory role in apoptosis, autophagy and migration, and Trib3 induces apoptosis by activating the NF-κB signaling pathway, the study by J. Su et al.[18] showed that emodin can induce apoptosis of lung cancer cells through ER stress and Trib3/NF- κB pathway.

3.3.3 Activation of enzymes to induce apoptosis

(1) Antioxidant enzymes：The peroxiredoxin (PRX) family is abnormally expressed in various tumors including gastric cancer. Among them, Prx V is considered to be an antioxidant enzyme that scavenges intracellular reactive oxygen species (ROS) and regulates apoptosis. Y.Z.Jin[5] studies have shown that emodin can induce apoptosis and reduce the expression of Prx V in AGS gastric cancer cells. （2）Cysteine aspartic protease: The experimental results of I.T. Saunders[19] showed that in colon cancer, emodin activates caspase, regulates the Bcl-2 protein family, reduces mitochondrial membrane potential, and induces colon cancer (COCA) cell death, while No obvious effect on normal colonic epithelial cells. (3) Fatty acid synthase (FASN)： FASN is a key enzyme in the synthesis of fatty acids and plays an important role in the occurrence and development of colon cancer. The results of K.H.Lee et al.[20] show that emodin can down-regulate the expression of FASN in HCT116 human colon cancer cells, inhibit the activity of FASN and the biosynthesis of fatty acids, and induce anti-proliferation and apoptosis of HCT116 cells.

3.4. Inhibition of tumor cell metastasis

Proteolytic enzymes play an important role in the occurrence, development and metastasis of tumors. Its members such as MMP-2, MMP-9 and uPA play an important role in breast cancer metastasis. Y.Sun et al.[6] found that emodin inhibited lung metastasis of human breast cancer, inhibited the invasion of MDA-MB-231 cells, decreased the expression of MMP-2, MMP-9, uPA and uPAR, and inhibited the activity of P38 and ERK in mouse xenograft model.

J. Lu et al.[21] found for the first time that emodin inhibits EMT in EOC cells by targeting ILK and inhibits intimal transduction in EOC cells through ILK/GSK-3 β / SLUG signal pathway. In addition, emodin inhibited the phosphorylation of glycogen synthase kinase 3 β (GSK-3 β), decreased the total protein level of β-catenin, and down-regulated the expression of transcription factor zinc finger E-box binding homeobox 1 (ZEB1). C.Hu 's research team[22] confirmed for the first time that emodin has anti-invasive effect on epithelial ovarian cancer A2780 and SK-OV-3 cells. The main mechanism is that emodin inhibits the invasion of EOC cells by inhibiting EMT and regulating GSK-3 β / β-catenin/ZEB1 signal pathway in vitro, thus inhibiting the invasion of EOC cells. Ilk is a factor that regulates extracellular matrix and cell-cell interaction by phosphorylating its downstream target kinases b/akt (PI3K/AKT) and gsk3 β. Ilk has been found to promote the metastatic behavior of ovarian cancer cells. J.Lu's study[23] has shown that emodin can enhance the proliferation, migration and invasion of ovarian epithelial cells by neutralizing Ilk in vivo and in vitro. In addition, emodin inhibits EMT of EOC cells by targeting Ilk, thereby inhibiting the migration and invasion ability of EOC cells.

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The infiltration and dissemination of tumor cells are related to the peri-tumor adipose tissue. Xiaoyun SONG and others[24] concluded through experiments that emodin can inhibit the secretion of ccl5 from adipocytes, inhibit the EMT of triple-negative breast cancer (TNBC) cells, and at the same time inhibit tumor growth and lung and liver metastasis, suggesting that emodin can prevent TNBC metastasis.

It has been found that mir-1271 can significantly inhibit the EMT and invasive ability of pancreatic cancer SW1990 cells. The experimental results of N. Li et al.[25] showed that emodin can increase the level of mir-1271, inhibit the EMT of pancreatic cancer cells, and inhibit the proliferation ability of pancreatic cancer cells. In addition, the research of J. Gu[26] and others suggested that emodin can significantly inhibit the expression of VEGF in RKO cells and colon cancer tissues, and reduce the expression of MMP-7 and MMP-9, suggesting that emodin can inhibit the metastasis of colon cancer cells.

Q. Liu et al.[27] showed that emodin can inhibit the typical and atypical transforming growth factor-β-1 signaling pathway in breast cancer cells, and inhibit the transcription factors related to the transformation and differentiation of breast cancer cells. Epithelial transformation and stellate cell formation in breast cancer cells, and propose that short-term preoperative application of emodin can reduce tumor-promoting macrophages and inhibit the formation of EMT and CSC in primary tumors, thereby preventing postoperative lung metastasis of breast cancer relapse.

3.5. Inhibition of angiogenesis

Vascular endothelial growth factor (VEGF) is a highly specific factor that promotes the growth of vascular endothelial cells. Vascular endothelial growth factor receptor specifically binds to vascular endothelial growth factor. VEGFR-1 and VEGFR-2 are mainly distributed on the surface of tumor vascular endothelium, which can promote tumor angiogenesis. Vascular development plays an important role in tumor growth and metastasis by transporting nutrients and oxygen to cancer cells. G.Zou[28] found that targeting transcriptional regulators NCOR2 and SerRS can inhibit VEGFA transcription and tumor angiogenesis, which has the potential to treat triple negative breast cancer (TNBC). In addition, J.Bai[29] has also shown that emodin can inhibit the occurrence of hepatocellular carcinoma by inhibiting VEGFR2-AKT-ERK1/2 signal pathway and promoting miR-34a-mediated signal pathway. Tumor necrosis factor receptor-associated factor 6 (TRAF6) is closely related to tumor angiogenesis and metastasis. G.H.Shi et al.[30] confirmed the relationship between TRAF6 and angiogenesis / metastasis in anaplastic thyroid carcinoma. The researchers further found that emodin inhibits TRAF6/HIF-1 α / VEGF and TRAF6/CD147/MMP-9 signal pathways in a concentration-dependent manner, and inhibits angiogenesis and metastasis in anaplastic thyroid carcinoma (ATC).

3.6. Reversing multidrug resistance and increasing tumor chemosensitivity

At present, chemotherapy is one of the most effective methods for the treatment of cancer, together with surgery and radiotherapy as the three major means to treat cancer. However, drug resistance to anticancer drugs is the main reason for the failure of chemotherapy for malignant tumors. Researchers began to look for combinations of drugs to reverse multidrug resistance and increase sensitivity to chemotherapy.

3.6.1 Breast cancer

The study of M. Bhattacharjee[7] showed that the combination therapy of thymoquinone and emodin can effectively promote breast cancer cell apoptosis, and reduce cell migration and stem cell number. Breast cancer stem cells have significant self-renewal ability, which has been found to be related to the drug resistance of breast cancer chemotherapy. The combined treatment of thymoquinone and emodin successfully reduced the number of D44+/CD24 cells, indicating that the synergistic effect of the two drugs may hinder the dry development of breast cancer

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MCF-7 cells. The efficacy of 5-fluorouracil is also limited in the clinical treatment of breast cancer due to its drug resistance. NRARP (Notch-regulated ankyrin repeat protein) is a negative feedback regulator protein in Notch signaling and is regulated by notch protein. NRARP was recently found to promote breast cancer cell proliferation and overexpression in breast cancer. The research of C. Zu et al.[31] has shown that emodin combined with 5-fluorouracil not only inhibits NRARP, but also induces tumor cell senescence, thus effectively improving the efficacy of chemotherapy for breast cancer. Salt-induced kinase 3 (SIK3) belongs to the family of AMPK-related kinases, which is involved in the regulation of cell metabolism, cell polarity remodeling and epithelial-mesenchymal transformation. The increased expression of SIK3 in breast cancer cells is related to tumorigenesis. L.Ponnusamy et al.[32] have found that berberine and emodin can inhibit the growth of breast cancer and promote apoptosis by inhibiting SIK3-induced mTOR and AKT signal pathways. Berberine has cytotoxic effect on tumor cells, but not on normal cells.

3.6.2 Pancreatic cancer

EGFR (epidermal growth factor receptor) is a member of the epidermal growth factor receptor (HER) family. EGFR is widely distributed on the surface of mammalian epithelial cells, fibroblasts, glial cells, keratinocytes and so on. EGFR signaling pathway plays an important role in cell growth, proliferation and differentiation. The overexpression of EGFR is closely related to the formation, metastasis and deterioration of tumors. However, the drug resistance of targeted therapy of EGFR inhibitors seriously affects its clinical application. In recent years, studies have shown that stat3 is an important downstream regulator of EGFR signaling pathway, involved in EGFR-mediated tumor cell proliferation and differentiation, and involved in the regulation of a variety of biological functions of EGFR. Z.Wang et al.[8] found that emodin can promote Afatinib-induced apoptosis by inhibiting stat3 signal pathway. It was also found that emodin combined with EGFR inhibitor lapatinib was superior to emodin or EGFR inhibitor alone in inhibiting cell proliferation. The results show that emodin combined with EGFR inhibitor is an effective therapeutic strategy to make human pancreatic cancer sensitive.

Gemcitabine is effective in patients with advanced pancreatic cancer, but patients usually develop drug resistance after taking gemcitabine for a few weeks, and there is evidence that NF-κ B may be the most important regulator. A recent study by H. Tong[33] has shown that emodin can reverse the drug resistance of pancreatic cancer cell lines by inhibiting the expression of Ikk β, inhibiting the expression and activity of downstream NF- κ B, and inhibiting the function of P-gp. Gemcitabine and emodin have synergistic anti-tumor effects in vivo and in vitro. Also, H. Guo[34] suggested that emodin may inhibit MDR1/glycoprotein P, MRP1 and MRP5 by expression, enhancing the anticancer effect of gemcitabine and reversing the resistance of pancreatic cancer to gemcitabine. Furthermore, because MDR1/ glycoprotein p, MRP1 and MRP5 proteins are involved in the development of resistance to other chemotherapeutic drugs, including 5-fluorouracil and cisplatin, emodin may also reduce or delay the resistance of pancreatic cancer to these drugs. Therefore, the addition of emodin in first-line chemotherapy may help to reduce chemotherapy resistance, improve the therapeutic effect, reduce the possibility of drug resistance, and further prolong the survival time of patients with pancreatic cancer.

Aberrant gene methylation is one of the important factors leading to tumorigenesis. 5-Aza-CdR is currently recognized as a demethylated drug. F.-P.Pan[35] has shown that emodin combined with 5-Aza-CdR can enhance the demethylation of tumor suppressor genes RASSF1A, P16 and ppENK in pancreatic cancer cells by reducing the expression of methyltransferase DNMT1 and DNMT3a.

3.6.3 Lung cancer

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Adriamycin resistance is a serious phenomenon in the treatment of lung cancer. Clinical treatment revealed that Shu Feng Jie Du capsule can effectively reverse the drug resistance of H69AR cells to adriamycin. Through the analysis of the composition of Y.Ying's team[36], emodin, as one of the main components of Shu Feng Jie Du capsule, plays an important role in reversing the drug resistance of lung cancer H69AR cells to adriamycin by inhibiting EMT.

Paclitaxel (PTX) is an effective drug in the treatment of NSCLC, but it also has serious side effects. S. Che, Z. Zhang[37] found that the combination of emodin and PTX could synergistically inhibit the proliferation of A549 cells. At the same time, emodin can also significantly enhance PTX-induced apoptosis of A549 cells by up-regulating the expression of Bax and active caspase3, and reducing the levels of Bcl-2, p-Akt and p-ERK. In addition, emodin could significantly enhance the anti-tumor effect of PTX on A549 transplanted tumor without obvious side effects.

3.6.4 Other cancers

(1) Bladder cancer: X.Li et al.[38] found that emodin can increase the level of reactive oxygen species (ROS) by reducing glutathione-cisplatin (gsh-ddp) conjugates, and effectively enhance the toxic effect of cisplatin on human bladder cancer t24 and j82 cells. The resistance of T24 and J82 cells to cisplatin was blocked by inhibiting the expression of MRP1. This effect is specific in T24 and J82 cells. Therefore, it can be considered that emodin can be used as an effective adjuvant for cisplatin-based bladder cancer chemotherapy to reduce bladder cancer recurrence.

(2) Ovarian cancer: K.Song 's team[12] found that the combination of emodin and cisplatin can reduce the growth of human ovarian cells by down-regulating the expression of multidrug resistance-associated protein 1.

(3) Liver cancer: Sorafenib is a first-generation multi-kinase inhibitor, and its efficacy often decreases in the treatment of advanced liver cancer (HCC). However, some studies have shown that emodin can enhance the anti-tumor effect of sorafenib and reduce cholesterol biosynthesis in vivo and in vitro by inhibiting tumor growth signal pathway and stat3-mediated cell cycle progression and proliferation. The experimental results of Y.-S.Kim[39] suggest that the combination of emodin and sorafenib may have a potential therapeutic effect on patients with advanced liver cancer.

3.7. Other anti-tumor mechanisms

Emodin can kill tumor cells in other ways: (1) Inhibit the development of inflammation: Y.Zhang[40] has shown that emodin can inhibit carcinogenic-related intestinal inflammation and prevent the occurrence and development of intestinal tumors induced by AOM/DSS. (2) Drive mitotic catastrophe: mitotic catastrophe is a kind of cell death caused by cell cycle disorder, abnormal chromosome segregation and cell division, which is similar to the process of apoptosis. As another type of cell death, mitotic catastrophe is an ideal process for anticancer therapy. W.Trybus[41] has shown that emodin can inhibit the change of mitotic cytoskeleton according to concentration and culture time, which leads to mitotic death of cervical cancer cells and becomes an alternative type of cancer cell death.(3) Promote autophagy of cancer cells: Mutational loss of function of p53 is a very common cause of human cancer, and wild-type p53 is a tumor suppressor protein essential for cancer prevention. The experimental results of E.Haque[42] showed that the autophagy level of lung cancer cells treated with 20 μ M emodin was significantly higher than that of normal cells, which may play a role in the removal of p53 protein aggregates in lung cancer A549 cells treated with emodin. Y. Wang et al.[43] also found that emodin could induce apoptosis in colon cancer cells by inducing autophagy, and emodin treatment led to mitochondrial dysfunction and accumulation of reactive oxygen species in colon cancer cells. Therefore, the researchers emphasized that the accumulation of reactive oxygen species is a necessary condition for emodin to induce autophagy and apoptosis.(4) Regulation of apoptosis gene: The results of C.Zu[44] show that emodin induces apoptosis of

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Bcap-37 and ZR-75-30 breast cancer cells in a dose-and time-dependent manner by regulating the expression of apoptosis-related genes.

4. SUMMARY AND PROSPECT

In summary, emodin has obvious anti-tumor effects and has obvious curative effects on breast cancer, cervical cancer, pancreatic cancer, colon cancer, liver cancer, lung cancer and other tumours. The main mechanism is to inhibit cell growth and proliferation, affect cell cycle, block signal pathway, inhibit cell invasion, inhibit cell EMT, inhibit angiogenesis, reverse multidrug resistance and increase chemosensitivity. Today, emodin can also be used as a potential therapeutic drug for prostate cancer[14], liver cancer[39] and other cancers. However, due to the lack of thorough research on some mechanisms at present, part of the anti-tumor effect of emodin is limited to in vitro experiments[12], and the effect on the human body is not accurate, which limits the clinical significance of the research results. In addition, literature[29] proposed that the heart and liver are potential targets of emodin, and the experimental results showed that relatively high concentrations of emodin were detected in these two tissues even after 12 hours of administration. In addition, the analysis of plasma protein binding ability and stability showed that emodin had a strong binding ability to plasma, and there were slight species differences. Therefore, further clinical experimental studies are needed to maximize the anti-tumor effect of emodin, and to evaluate the safety and stability of emodin's anti-tumor effect, so as to make its clinical use safer and more reliable.

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