ISSN 2618-1584 Vol. 5, Issue 8: 74-78, DOI: 10.25236/FMSR.2023.050810

Research Progress on the Mechanism of Evodiamine against Hepatocarcinoma

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Abstract: *China is a region with high incidence of liver cancer. The incidence of liver cancer accounts for more than 50% of the global incidence. As early as in the "Shengnong Herbal Classic" recorded: " warms qi in the middle, pain relief, cough against cold and heat, dehumidification, blood bi, wind evil, open Zou Li." Modern pharmacological studies have shown that Evodiamine can significantly inhibit the proliferation of cancer cells, promote the apoptosis of cancer cells, block the cycle of cancer cells, and inhibit the invasion and metastasis of liver cancer cells. At present, studies on the mechanism of Evodiamine's anti-liver cancer action mainly focus on several pathways, and most of them are cell and animal experiments. The effective components and dose-effect relationship of Evodiamine against tumor are not perfect, and relevant studies on drug-fast and body immunity are lacking. In the future, the above points can be further studied to provide a new scientific basis for clinical application.*

Keywords: *liver cancer, evodiamine, mechanism of action, review*

1. Introduction

Liver cancer is highly prevalent in China, with over 50% of global liver cancer cases occurring in the country. According to data released by the National Cancer Center, the number of liver cancer cases in China is approximately 388,800, ranking it as the fourth most common malignant tumor in the country. The number of deaths caused by liver cancer is approximately 336,400, making it the second leading cause of cancer-related deaths in China [1]. The disease has a low cure rate and a high recurrence rate, with many patients facing treatment difficulties due to local recurrence or metastasis. Although various treatment methods for primary liver cancer, such as surgical resection, liver transplantation, and local ablation therapy, have rapidly developed in recent years, and new chemotherapy drugs have been approved for market, chemotherapy drugs still have significant side effects and poor selectivity, discouraging people from seeking treatment and making the treatment situation extremely challenging. In the theoretical framework of traditional Chinese medicine, the etiology of liver cancer mainly involves deficiencies in Qi, Blood, Yin, Yang, Qi stagnation, Blood stasis, and Damp-Heat. Treatment methods include tonifying Qi and invigorating the Spleen, nourishing the Liver and Kidneys, regulating Liver Qi, promoting blood circulation and resolving stasis, clearing heat and detoxifying, and others [2]. Wu Zhu Yu, which belongs to the liver meridian and has the functions of reducing counterflow and stopping vomiting, and assisting Yang and stopping diarrhea, plays a certain role in regulating Liver Qi [3]. Ye Tianshi, a famous Warm Disease physician during the Qing Dynasty, had a profound understanding of tumor treatment. Through statistical analysis of the 127 Chinese medicinal herbs used in Ye Tianshi's 87 prescriptions, it can be concluded that the core combination of medicines used by Ye Tianshi consists of Fu Ling (Poria cocos) and Wu Zhu Yu, with an 88.9% probability of Wu Zhu Yu appearing in prescriptions containing Fu Ling [4]. Modern pharmacology indicates that Wu Zhu Yu alkaloids have analgesic, anti-inflammatory, anti-tumor, and antioxidant properties, exerting physiological activities on the cardiovascular system, central nervous system, digestive system, reproductive system, and others. This study collected and analyzed relevant literature on the anti-liver cancer mechanisms of Wu Zhu Yu alkaloids in the past decade, summarizing and categorizing the research progress on their mechanisms of action, providing a scientific basis for exploring the molecular mechanisms of the anti-liver cancer effects of Wu Zhu Yu alkaloids in future studies.

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2. Inhibition of Hepatocellular Carcinoma Cell Proliferation

Cell proliferation is the foundation of cell growth and development. However, excessive proliferation of cells that are not regulated by genes has become an important basis for cancer cell growth. Compared with other normal cells, one of the characteristics of tumor cells is to accept continuous proliferation signals and achieve proliferation and immortalization. Therefore, effective inhibition of tumor growth is one of the functions of anticancer drugs.

Che Yuan et al. [5] found that the expression of WWOX increased in a dose-dependent manner to exert its anti-liver cancer effect by treating hepatoma cell lines HepG2 and Hepa1-6 mice with evodiamine. In addition, through the studies conducted by YuPu Li [6] and Zhenzhen Wen [7], we understand that the downregulation of WWOX in liver cancer cells leads to the accumulation of β-catenin in the cytoplasm, activating the Wnt/β-catenin signaling pathway. The decrease in Akt and GSK-3β activities inhibits the expression of β-catenin. Furthermore, Evodiamine can suppress the Wnt/β-catenin signaling pathway to inhibit cancer cell proliferation and exert its anticancer effects by reducing Akt signaling pathway phosphorylation. Based on the research findings of these three authors, it can be inferred that Evodiamine may inhibit liver cancer cell proliferation and exert its anticancer effects through the activation of WWOX. Additionally, hypoxic microenvironments are commonly present in liver cancer cells, promoting cell proliferation, metabolism, angiogenesis, invasion, metastasis, and resistance to treatment [8]. The study by Yang ling Li et al. [9] demonstrates that Evodiamine may enhance the anti-liver cancer cell growth and metastasis effects of fulvestrant by accelerating the degradation of hypoxia-inducible factor-1α under hypoxic conditions. De Chengchao et al. [10], in their study on Zuojin Pill and its alkaloids, found that Evodiamine primarily inhibits the growth of liver cancer cells by suppressing the AP-1 and NF-κB signaling pathways. YAP is a key transcription factor downstream of the Hippo signaling pathway. It is an oncogene that can bind to downstream transcription factors, promoting cell proliferation and inhibiting cell apoptosis, leading to tumor development. Research conducted by Zhao Shuang et al. [11-12] revealed that Evodiamine can promote the phosphorylation of YAP in the Hippo-YAP signaling pathway and reduce its nuclear expression by Brown R[13], thus regulating the proliferation and apoptosis of liver cancer cells.

3. Promotion of Hepatocellular Carcinoma Cell Apoptosis

Apoptosis, or programmed cell death, is a natural cellular process aimed at eliminating unnecessary or damaged cells within the body. In healthy tissues, there exists a well-regulated balance between pro-apoptotic and anti-apoptotic proteins, which collectively regulate cell apoptosis. However, cancer cells upregulate the expression of anti-apoptotic proteins to suppress cell apoptosis, ultimately leading to tumor growth, poor prognosis, and drug resistance. Apoptosis can be categorized into three major pathways based on the different initiation stages: the mitochondrial pathway, endoplasmic reticulum pathway, and death receptor pathway. These pathways interact and interconnect to jointly regulate the process of apoptosis. The Bcl-2 gene, as an oncogene, plays a role in inhibiting cell apoptosis, and some mechanisms have been revealed through recent research. The Bcl-2 protein family, which includes Bcl-2 with an anti-apoptotic function and Bax with a pro-apoptotic function, can be classified into two categories based on their functions.

In the study by Un Jung Yun et al. [14], Evodiamine was found to reduce the levels of YAP/Bcl-xL in liver cancer cells, inducing mitochondrial dysfunction-mediated cell apoptosis. Additionally, the research findings of Li Caiyun [15] demonstrated that Evodiamine can upregulate the expression levels of pro-apoptotic proteins, such as Cleaved caspase3 and cleaved PARP, while downregulating the expression level of the anti-apoptotic protein Bcl-2, thereby promoting apoptosis in liver cancer cells through the P-ERK and P-p38 pathways in the MAPK pathway. Guo Xingxian et al. [16-17], in their in vitro and in vivo studies, showed that Evodiamine inhibits the proliferation of liver cancer cells and induces apoptosis by suppressing the expression of NOD1, which subsequently inhibits the activation of NF-κB and MAPK. Furthermore, the research by Fan Yang [18] demonstrated that Evodiamine may exert its anticancer effects in liver cancer cells by inducing Akt-mediated apoptosis.

4. Inhibition of Hepatocellular Carcinoma Cell Cycle Progression

The cell cycle is typically divided into four phases: G1 phase (pre-DNA synthesis phase), S phase (DNA synthesis phase), G2 phase (post-DNA synthesis phase), and M phase (mitosis). There is a close association between the cell cycle and tumorigenesis. During the cell cycle process, a complex signaling

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network of cell cycle proteins (cyclins), cyclin-dependent kinases (CDKs), and cyclin-dependent kinase inhibitors (CKIs) regulates the cell cycle. This signaling network forms the basis for proper cell cycle progression. Any abnormalities in cell cycle regulation can lead to abnormal cell proliferation and differentiation, ultimately resulting in tumor formation and progression.

The research findings by Li Caiyun [15] indicate that Evodiamine significantly upregulates the expression of Cyclin B1, which is closely associated with the G2/M phase. This leads to the arrest of liver cancer cells at the G2/M phase, thereby exerting its inhibitory effect on liver cancer cells. The JAK-STAT (Janus kinase-signal transducer and activator of transcription) signaling pathway is closely involved in the regulation of proliferation, differentiation, apoptosis, and immunity in cells and has a significant relationship with various cancers [19]. Jie Yang et al. [20], through in vitro and in vivo studies, found that Evodiamine can block the STAT3 pathway through two different mechanisms. One is by inducing SHP-1, and the other is by inhibiting the activation of upstream kinases of STAT3. Inhibiting STAT3 phosphorylation can downregulate gene products associated with cell survival and cell cycle progression, thereby inducing cell apoptosis and cell cycle arrest.

5. Inhibition of Hepatocellular Carcinoma Cell Invasion and Metastasis

Although primary tumors can be highly dangerous, most cancer patients eventually die due to the growth of metastatic tumors in distant sites from the primary tumor. This metastasis often occurs when cancer cells from the liver cancer leave the liver and spread throughout the body via the rich blood and lymphatic vessels in the liver. In the research findings by Un Jung Yun et al. [14], Evodiamine was shown to block the stromal characteristics of liver cancer cells, inhibiting their invasion and metastatic properties.

Furthermore, the in vitro and in vivo studies by Hanzhang Zhu et al. [21] demonstrated that Evodiamine inhibits the expression of PRAME (preferentially expressed antigen in melanoma) by tri-methylating H3K27, thereby exerting its ability to suppress tumor cell metastasis.

By blocking the invasive and migratory properties of liver cancer cells and inhibiting the expression of PRAME, Evodiamine plays a role in inhibiting the spread of cancer cells and their ability to form metastatic tumors.

6. Studies related to evodiamine derivatives

In order to enhance the anti-tumor activity of a compound, it is common to perform structural modifications and obtain its derivatives. In the research conducted by Fang Lei et al. [22], several N14-phenyl substituted derivatives of Evodiamine were obtained. Among them, compounds F-3 and F-4 exhibited dual inhibition of topoisomerase I and II, suppressed invasion and migration, blocked the cell cycle at the G2/M phase, and induced cell apoptosis. Additionally, compounds F-3 and F-4 were able to inhibit the activation of HSC-T6 cells and reduce the secretion of type I collagen, thus slowing down the progression of liver fibrosis. In comparison with positive drugs in experimental studies, compound F-4 showed more significant inhibition of tumor growth compared to the positive drug Sorafenib.

Similarly, Xiaohong Fan et al. [23] designed and synthesized 15 Evodiamine derivatives that simultaneously target Topoisomerase I and cancer-associated fibroblasts (CAFs) for inhibiting liver cancer cells. Among them, compound number 8 induced significant G2/M arrest and cell apoptosis, significantly reduced the migration and invasion ability of HCC cells, downregulated the expression of type I collagen in activated HSC-T6 cells, and induced apoptosis in activated HSC-T6 cells. In in vivo studies, it exhibited better tumor inhibition effects compared to Evodiamine.

These studies demonstrate that the derivatives of Evodiamine, such as F-3, F-4, and compound number 8, possess enhanced anti-tumor activities by targeting multiple pathways, inhibiting tumor growth, and suppressing cancer cell invasion and migration.

7. Conclusion

As one of the classic Chinese medicine, Evodiamine can inhibit different tumors through multiple pathways, multiple pathways and multiple targets. Although modern pharmacological experiments have found a variety of molecular mechanisms of Evodiamine in the treatment of liver cancer, there are still some shortcomings. First, current studies are all based on cell and animal studies, and relevant clinical studies are still blank. Second, studies on the anti-liver cancer effect of Evodiamine are still focused on

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the molecular action of a single pathway. For treatment, it is often the result of the interaction of various pathways, and further studies on relevant pathways and targets are needed. The molecular mechanism of Evodiamine against hepatocellular carcinoma cells was described.

Data sharing agreement

The datasets used and/or analyzed during the current study are available from the corresponding aut hor on reasonable request.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, author-ship, and/or publication of this article.

Acknowledgement

The author(s) received no financial support for the research.

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