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Research Progress of Curcumin and Its Derivatives in the Treatment of Hepatocellular Carcinoma: From Natural Product to Candidate Drugs

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Abstract. Hepatocellular carcinoma (HCC) stands for a type of malignant neoplasm that is among the most commonly occurring and highly lethal ones on a global scale. Current treatments suffer from limitations such as drug resistance and significant side effects, necessitating the development of novel therapeutic drugs. Curcumin, a natural polyphenol compound, can exert multi-target anti-hepatocellular carcinoma effects by inhibiting HCC cell proliferation, inducing apoptosis, blocking metastasis, and regulating multiple signaling pathways, including NF-κB and PI3K/Akt. However, the low bioavailability and metabolic instability of curcumin have hindered its clinical translation. Current research mainly focuses on developing derivatives through structural modification, constructing nanodelivery systems, or achieving synergistic sensitization through combination with drugs such as sorafenib. In summary, through structural optimization and innovative delivery technologies, curcumin and its derivatives hold promise for gradually evolving from natural products into candidate anti-hepatocellular carcinoma drugs, possessing significant clinical value.

Keywords: Curcumin, Hepatocellular carcinoma, Nanodelivery systems

1. Introduction

Hepatocellular carcinoma (HCC) is included in the category of the most commonly occurring malignant neoplasms across the world. In the process of considering the frequency of cancer diagnoses, it ranks as the sixth most frequently diagnosed cancer. And in the process of looking at the causes of cancer - related deaths, it is the third leading cause of cancer - related situations mortality globally. Its pathogenesis is closely related to various chronic liver diseases, especially chronic viral hepatitis (such as hepatitis B and C), cirrhosis, and non-alcoholic fatty liver disease [1]. Currently, treatment methods for liver cancer include surgical resection, targeted drug therapy, liver transplantation, and chemotherapy. However, existing treatment methods have many limitations: firstly, early diagnosis of liver cancer is difficult, and most patients miss the optimal treatment window; secondly, targeted drugs are expensive and have significant side effects, and are prone to

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drug resistance, leading to a high recurrence rate [2]. Therefore, exploring novel, highly effective, and low-toxicity treatment strategies is an urgent problem to be solved.

In recent years, natural products, due to their diverse structures and low toxicity, have become an important source for the development of novel anticancer drugs. Curcumin, a yellow polyphenol extracted from the rhizome of turmeric, exhibits a wide range of biological activities, and its potential in combating hepatocellular carcinoma has attracted increasing attention. Curcumin not only possesses basic activities such as anti-inflammatory and antioxidant effects, but also, by acting on multiple targets, can effectively inhibit cancer cell proliferation, induce apoptosis, and prevent metastasis, demonstrating strong anticancer potential [3].

However, curcumin itself also has significant drawbacks. Its poor water and lipid solubility leads to poor oral absorption and low bioavailability. Furthermore, curcumin is rapidly metabolized in vivo and easily eliminated [4,5]. Therefore, overcoming these problems and improving the efficacy of curcumin has become a key focus of current research. This review summarizes the pharmacological activities and underlying molecular mechanisms of curcumin in HCC treatment, with a focus on two key strategies developed in recent years to overcome its shortcomings—designing novel derivatives and constructing delivery systems—and looks forward to the future development direction of curcumin in liver cancer therapy.

2. Pharmacological effects and core mechanisms of curcumin against hepatocellular carcinoma

The core advantage of curcumin in fighting hepatocellular carcinoma lies in its mechanism of action, which is not limited to a single target but rather works by regulating a complex cellular signaling network to collectively inhibit the occurrence and development of liver cancer against multiple targets. Recent studies have shown that curcumin can simultaneously act on multiple key processes, including cell proliferation, apoptosis, metastasis, and angiogenesis, exhibiting a multi-target, multi-pathway effect. The following describes the pharmacological effects and underlying mechanisms of curcumin in fighting liver cancer.

2.1. Inhibition of hepatocellular carcinoma cell proliferation

Curcumin effectively regulates the cell cycle of hepatocellular carcinoma cells. It stabilizes the cell cycle by activating the AMPK signaling pathway, inhibiting cell cycle progression and ultimately arresting hepatocellular carcinoma cells in the G1 phase. Furthermore, curcumin has the ability to carry out an action on the membrane structure as well as the cytoskeleton of hepatocellular carcinoma cells to disrupt them. This disruption then leads to a situation where the cell cycle of these cells gets arrested at the G2/M phase. And after that, it further goes on to block the process of cell division [6,7].

2.2. Induction of hepatocellular carcinoma cell apoptosis

Curcumin takes on a role that is of crucial significance in the process of causing the occurrence of apoptosis in hepatocellular carcinoma cells. It can induce a decrease in mitochondrial membrane potential and activate the Caspase family by upregulating the pro-apoptotic protein Bax and downregulating the anti-apoptotic protein Bcl-2, thereby initiating the apoptotic program in hepatocellular carcinoma cells and promoting programmed cell death [8].

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2.3. Inhibition of hepatocellular carcinoma metastasis and angiogenesis

Metastasis stands as a major contributing factor that leads to the high mortality rate among patients with hepatocellular carcinoma (HCC) [9]. In the process of the biological activities within HCC, it has been well - documented that when the TGF - β signaling pathway undergoes the process of activation, this activation event causes the up - regulation of the expression of matrix metalloproteinases (MMPs). Then, after the expression of MMPs is up - regulated, it results in the enhancement of the migratory capacity and the invasive capacity of HCC cells. Curcumin can effectively block this process and inhibit hepatocellular carcinoma metastasis by reducing MMP activity [10]. In addition, curcumin also inhibits tumor angiogenesis by downregulating the expression of vascular endothelial growth factor, thereby reducing the oxygen and nutrient supply to the tumor and inhibiting the growth and progression of liver cancer [11].

2.4. Regulation of multiple signaling pathways

Multiple core signaling pathways in liver cancer cells can be precisely modulated by curcumin, which underlies its well-documented anti-cancer effects. Specifically speaking, curcumin has the ability to effectively carry out the action of suppressing the situation where the NF - κB signaling cascade is in a state of constitutive activation. In this way, it can achieve the effect of alleviating the inflammatory tumor micro - environment and also promote the process of the apoptotic death of HCC cells [12]; it also inhibits the PI3K/Akt signaling pathway, thereby blocking cancer cell proliferation and inducing apoptosis [11,13]; furthermore, curcumin can regulate the Wnt/β-catenin pathway, restoring its normal regulation, and thus inhibiting the occurrence of liver cancer [14].

3. Development of curcumin derivatives and drug delivery systems

Although curcumin exhibits multi-target and multi-pathway pharmacological advantages in combating hepatocellular carcinoma, its inherent limitations, such as poor water solubility, rapid metabolism under physiological conditions, and low systemic bioavailability, severely restrict its clinical translation process.6 To overcome this bottleneck, current research mainly revolves around two core strategies: first, to synthesize curcumin derivatives with superior activity and drug-like properties through rational chemical structural modification; and second, to construct novel drug delivery systems to improve its pharmacokinetic characteristics and tumor targeting.

3.1. Structurally modified derivatives

To improve the stability and bioactivity of curcumin, researchers, based on the key deficiency of its unstable β-diketone structure, synthesized a series of monocarbonyl analogs and heterocyclic derivatives through structural modification. Among them, EF24 is the most extensively studied curcumin analog to date. By removing the unstable β-diketone group and introducing a piperidone structure, it significantly improved water solubility and in vitro metabolic stability, and its efficacy in inhibiting liver cancer cell proliferation and inducing apoptosis was several times that of the parent compound [15]. In addition, naturally occurring analogs such as demethoxycurcumin and bisdemethoxycurcumin exhibited better selectivity indices while maintaining antitumor activity [16]. Recent studies have also found that derivatives with nitrogen-containing heterocyclic or aromatic ring substituents can further enhance the anti-liver cancer effect by increasing the activity of topoisomerase or kinase inhibitors. These studies illustrate that through the process of rationally carrying out the design of the curcumin core structure, its pharmacological efficacy has the potential

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to be significantly enhanced while the situation of retaining its multi - target advantages is maintained. This kind of situation lays a solid pre - clinical foundation for the process of developing novel anti - HCC drug candidates.

3.2. Novel nanodelivery systems for curcumin

Nanomedicine delivery systems are currently a mainstream research direction for overcoming the drug-like defects of curcumin. By encapsulating curcumin in liposomes, polymer nanoparticles, micelles, albumin nanoparticles, or inorganic nanocarriers, its dispersibility and stability can be significantly improved, and its circulating half-life in vivo can be prolonged [17]. Research not only focuses on increasing drug loading capacity but also emphasizes achieving intelligent release in response to the tumor microenvironment. For example, a study constructed a composite delivery system co-encapsulating curcumin and gold nanoparticles. This system utilizes the high specific surface area of gold nanoparticles to achieve a drug loading rate as high as 47.16% and can trigger rapid drug release in the acidic tumor microenvironment by leveraging the pH-sensitive material properties [18]. In addition to passive targeting based on enhanced penetration and retention effects, active targeting delivery systems modified with ligands, such as those modified with folic acid, galactosylation, or RGD peptides, have also been widely explored in recent years. These systems can accurately identify receptors overexpressed by liver cancer cells, further improving therapeutic selectivity and reducing systemic toxicity [19].

3.3. Combination strategies and chemosensitizing effects

Besides using delivery systems or derivatives alone, curcumin and its derivatives have also demonstrated good synergistic sensitization effects in combination therapy. Preclinical studies have confirmed that curcumin, when used in combination with sorafenib, a first-line targeted drug for liver cancer, can enhance the latter's killing effect on liver cancer cells through a multi-mechanism synergistic effect and effectively delay or partially reverse acquired drug resistance. Its sensitization mechanism involves multiple aspects: on the one hand, curcumin can suppress the expression of multidrug resistance-related proteins represented by P-glycoprotein, reducing sorafenib efflux; on the other hand, curcumin is able to carry out the action of abrogating the survival advantage of tumor cells by way of blocking the persistent activation of the NF - κB signaling pathway. Moreover, it can synergistically trigger the occurrence of intracellular oxidative stress as well as DNA damage [20,21]. This combination therapy strategy based on multi-target regulation not only offers a new strategy to address the drug resistance challenge in the clinical treatment of liver cancer, but also opens up a feasible path for the translational application of curcumin-like compounds as chemosensitizers for adjuvant chemotherapy.

4. Conclusion

Although curcumin and its derivatives have demonstrated multi-target and multi-pathway pharmacological advantages in anti-hepatocellular carcinoma research, their clinical translation still faces several core challenges. Firstly, most studies remain at the level of in vitro cell experiments and animal models, lacking large-scale, standardized clinical trials to verify their safety and efficacy. Secondly, while nanocarriers can improve the bioavailability of curcumin, its long-term in vivo distribution, metabolic pathways, and potential immunogenicity still require comprehensive evaluation. Furthermore, the efficiency of precise tumor-targeted delivery still has significant room

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for improvement, and the optimization of the structure-activity relationship of derivatives and the evaluation system for in vivo drug-likeness still need refinement.

To address these issues, research in this field can be further expanded in the following directions: Firstly, developing more intelligent and responsive delivery platforms, such as designing controllable release systems based on the tumor microenvironment to achieve precise spatiotemporal regulation; secondly, exploring the combined application of curcumin derivatives and immunotherapy to enhance anti-tumor immune responses by regulating the tumor immune microenvironment; and thirdly, utilizing artificial intelligence-assisted technology to conduct rational design and virtual screening of curcumin derivatives to obtain candidate molecules with excellent activity, selectivity, and drug-likeness.

In summary, curcumin, as a natural multi-target lead compound, demonstrates significant potential in hepatocellular carcinoma research. Through synergistic enhancement of its chemical structure and advanced drug delivery technologies, its inherent limitations can be overcome, propelling this class of compounds from basic research to clinical drug candidates. Future efforts should focus on strengthening interdisciplinary collaboration, deepening mechanistic research and translational exploration, to realize greater clinical value for this traditional natural product in modern liver cancer treatment.

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