The Application and Progress of Natural Bioactive Constituents in Liver Cancer

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***Abstract*—Liver cancer has been plaguing the world with its high incidence and mortality rates. Existing targeted therapy, immunotherapy, and chemotherapy have shortcomings such as drug resistance, obvious adverse reactions, and limited efficacy, so there is an urgent need to develop new treatment strategies. Natural Bioactive Constituents (NCBs) have become a research hotspot in liver cancer due to their multi-target, multi-pathway, and low-toxicity characteristics. This article searched relevant databases and systematically reviewed the anti-liver cancer mechanisms of active ingredients in natural medicines, including cell cycle regulation, induction of apoptosis, and ferroptosis. At the same time, it explored the application value of the combined strategy of NCBs. It also summarizes the innovative applications of passive, active, and physicochemically targeted delivery systems in overcoming the physicochemical drawbacks of natural drugs and enhancing their bioavailability.**

***Keywords*—natural bioactive constituents, liver cancer, treatment mechanism, delivery system, combination**

I. Introduction

Siddhartha Mukherjee's statement in "The Emperor of All Maladies: A Biography of Cancer" that "cancer is a highly successful invader and colonizer" accurately summarizes the current burden of cancer [1]. In 2022, there were 316,500 deaths from primary liver cancer in China, with the mortality rate ranking second among malignant tumors (lung, liver) [2]. If the global trend of liver cancer incidence remains unchanged, there will be 1.52 million new cases and 1.37 million deaths from liver cancer by 2050 [3]. Therefore, it is urgent to explore and develop new treatment strategies with better efficacy and more controllable costs. Natural Bioactive Constituents (NCBs) have attracted widespread attention due to their multi-target, multi-pathway, and low-toxicity characteristics. However, current research is limited by problems such as fragmented mechanistic explanations, unoptimized delivery systems, and a lack of systematic exploration of combination strategies. Based on literature from the past six years, this article reviews the progress of natural products against liver cancer, the optimization of delivery systems, and synergistic therapeutic effects, providing a reference for future research.

II. The Mechanism of NCBs Combating Liver Cancer

A. Inhibiting the Proliferation of Liver Cancer Cells and Inducing Autophagy and Apoptosis

NCBs can inhibit the proliferation of liver cancer cells by targeting key regulatory molecules of the cell cycle and blocking the cell cycle progression. At the same time, they can activate autophagy- and apoptosis-related pathways, initiate programmed cell death, and further induce autophagy and apoptosis in liver cancer cells. Arnicolide C (AC) induces G2/M phase cell cycle arrest in liver cancer cells by down-regulating the expression of Cyclin B1 and Cdc25c [4]. Quercetin 7-Rhamnoside (Q7R) downregulates the core target DHRS13 in liver cancer cells, thereby reversing DHRS13-mediated apoptosis inhibition, inducing apoptosis and inhibiting liver cancer cell proliferation [5]. Icaritin acid can induce liver cancer cells to undergo PINK1-Parkin-mediated mitochondrial autophagy and apoptosis, and inhibition of mitochondrial autophagy can significantly enhance its pro-apoptotic and anti-tumor effects [6].

B. Ferroptosis

Ferroptosis is a novel type of cell death that relies on iron ions and is triggered by the accumulation of large amounts of lipid peroxides. It holds significant importance in the intervention of liver cancer. GPX4 is a key antioxidant protein that regulates ferroptosis, and its stability is strictly regulated by ubiquitination modification. In a prospective study by Jiang *et al*. [7], ginsenoside CK was verified to inhibit the deubiquitinating enzyme OTUB2, promote GPX4 degradation, disrupt the cellular antioxidant system, and thereby induce ferroptosis in liver cancer cells, providing a novel mechanism for natural products in liver cancer therapy.

C. Inhibiting the Invasion, Metastasis, and Recurrence of Liver Cancer

Liver cancer is characterized by frequent invasion and distant metastasis, which are key factors leading to poor

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therapeutic efficacy and prognosis. The abnormal adhesion and invasion ability of tumor cells play an important role in metastasis. The natural flavonoid luteolin can downregulate highly expressed miR-6809-5p in liver cancer tissues, modulate the miR-6809-5p/FLOT1/FAK and PI3K/AKT/mTOR pathways, and affect the expression of EMT-related markers. It significantly inhibits the invasion, metastasis, and epithelial-mesenchymal transition of liver cancer cells in both in vitro and in vivo experiments [8].

D. Inhibition of Angiogenesis

Tumor invasion and metastasis disrupt the provision of nutrients and transfer channels by new blood vessels [9]. Natural drugs can inhibit angiogenesis-related signaling pathways and reduce the formation of new blood vessels in tumors, exerting anti-liver cancer effects. Genipin, as an anti-inflammatory natural product, acts independently of the HIF-1α pathway, but inhibits TLR4, blocks TLR4/MyD88 signal, down-regulates STAT3/Sp1 mediated VEGF secretion, inhibits angiogenesis and endothelial migration, and inhibits proliferation, invasion and lung metastasis of liver cancer with low toxicity [10].

E. Combined Multi-Drug Reduction of Toxicity and Enhancement of Efficacy, as well as Reversal of Drug Resistance

Active components from natural medicines can increase chemosensitivity, reduce toxicity, enhance the tumoricidal effect of chemotherapy, and reverse drug resistance. In the clinical treatment of advanced Hepatocellular Carcinoma (HCC), several bottlenecks remain: the efficacy of the targeted drug sorafenib is significantly limited by drug resistance [11]; Immune Checkpoint Blockade (ICB) is associated with issues such as insufficient targeting, autoimmune reactions, and individual differences [12, 13]; CRISPR/Cas9-mediated ICB gene therapy is constrained by the immunosuppressive microenvironment and low response rate [14]; the FOLFOX4 regimen is prone to drug resistance, reduced sensitivity, and toxic side effects [15–18]. Monotherapy is difficult to meet clinical needs, so safe and effective combination strategies urgently need to be developed. Natural medicine active components can achieve reduction of toxicity and enhancement of efficacy, as well as reversal of drug resistance through pathway complementation, target synergy, and remodeling of the tumor microenvironment. Icaritin (ICT) and Acetyl-11-Keto-β-Boswellic Acid (AKBA) can inhibit the JAK/STAT3 and PI3K/AKT pathways, downregulate stemness-related proteins, and reverse sorafenib resistance in liver cancer [11]; ursolic acid can improve the immunosuppressive microenvironment and combine with CRISPR/Cas9-mediated PD-L1 gene editing to synergistically enhance anti-cancer effects [13]; Acteoside (ACT) can alleviate oxaliplatin-induced neurotoxicity, reverse drug resistance, enhance chemosensitivity, and improve the efficacy of combination therapy [18].

III. Innovation of Targeted Delivery Systems for Natural Drug Active Components

Although natural drug active components possess excellent pharmacological activities, their clinical application is severely constrained: most of these compounds have poor water solubility, extremely low bioavailability, rapid metabolism, wide distribution, and difficulty in concentrating at tumor sites. Moreover, they lack targeting properties and are prone to damage to normal tissues. However, nano-targeted delivery systems for active components from natural medicines, which utilize carriers such as liposomes, nanoparticles, and micelles, can significantly improve drug solubility and stability through surface modification and responsive design. These systems can achieve precise targeting and controlled release through the EPR effect or ligand-receptor interactions, effectively overcoming the pharmacokinetic drawbacks of natural drugs.

A. Passive Targeting

Passive targeting is a delivery strategy that relies on the size-dependent retention and phagocytosis of particles by the body's tissues, organs, and reticuloendothelial system to achieve the natural enrichment of drugs in the target organs or lesion sites. Its core is that the drug-loaded particles are taken up by the mononuclear-macrophage system and preferentially distributed to organs such as the liver and spleen through physiological pathways. Liposomes, nanoparticles, microspheres, microemulsions, etc., can all be used for passive targeting delivery of natural drug active ingredients, effectively increasing the drug concentration at the target site and reducing systemic toxicity.

In the study of anti-liver cancer delivery, aiming at the problem of large toxic side effects of Adriamycin (DOX) and limited efficacy of single chemotherapy, researchers used Diosgenin (Dios) as a membrane regulator to construct DoXI-loaded Dios-based liposomes, which could improve the water solubility of the drug, enrich in the tumor through passive targeting, and synergitic and attenuated toxicity. This approach provides new insights for combined chemotherapy in liver cancer [19]. Dehydroxystilbene (DEM) can increase white blood cell counts and inhibit tumor proliferation, but it has poor targeting ability and high toxicity, limiting its clinical application. Researchers constructed DEM-based Nanoemulsion-based Lipid Nanoparticles (DNLNs), using the EPR effect to achieve passive targeting, to improve the distribution of tumor drugs and reduce damage to normal organs, providing a new strategy for DEM transformation [20]. To address issues such as low solubility and poor bioavailability of silybin and curcumin, a nanoprecipitation method was used to co-encapsulate these two compounds with silybin seed extract. The resulting nanoformulations achieved passive targeting through an appropriate particle size, improving stability and in vivo bioavailability, and providing a feasible solution for the targeted delivery of natural drugs to liver cancer [21].

B. Active Targeting

Active targeting is one of the core innovative directions of the active delivery system for natural drug active components. It achieves the active concentration and selective delivery of natural drug active components at the target site through precise binding of ligands to specific receptors on the surface of target cells, effectively addressing the problems of poor targeting and low bioavailability of natural drugs, and providing key technical support for the clinical application of natural drugs.

The Gal24 Sil active targeting delivery system is composed of a Galactose-modified dendrimer (Gal24) and silybin. Through the specific binding of galactose to the sialylated glycoprotein receptor on liver cancer cells, the drug is precisely enriched in HepG2 and Hep3B cells. This system improves silybin solubility and enhances anti-liver cancer efficacy by inducing inflammation, Reactive Oxygen Species (ROS) production, and mitochondrial membrane potential depolarization, expanding the application scope of the Gal24 carrier [22].

Wang *et al*. [23] also constructed ASP-BBR-PM@HNK micelles loaded with Honokiol (HNK), which possess both the liver-targeting ability of Astragalus Polysaccharide (ASP) and the mitochondrial-targeting ability of Berberine (BBR), forming a dual active targeting delivery system. These micelles can be efficiently internalized by HepG2 cells, exhibit GSH-responsive drug release and good stability, and significantly enhance the anti-liver cancer efficacy of HNK.

All of these provide innovative and feasible nanoscale platforms for the active targeting delivery of natural drugs against liver cancer.

C. Physical-Chemical Targeting

Physical-Chemical targeting is an important innovative branch of the active ingredient delivery system for natural drugs. It utilizes external physical stimuli, such as light, heat, magnetism, and ultrasound, or the body's internal chemical environment, such as differences in pH and redox status, to achieve precise localization and stimuli-triggered release of active components from natural medicines at the target site. This not only avoids the drawbacks of the easy degradation and insufficient targeting of natural drugs, but also further improves the delivery efficiency and reduces systemic toxic side effects. It is an important innovative strategy bridging passive targeting and active targeting.

Liu *et al*. [24] innovatively constructed a Chitosan (CS)/Pectin (PT) shell-structured composite nanoparticle (APs-CS/PT-NPs) oral colon-targeted delivery system, which utilizes the pH responsiveness of CS/PT and intestinal microbiota-mediated degradability to achieve specific release of APs at the colon. This system can precisely regulate the intestinal microbiota, increase the level of acetic acid, inhibit the Nuclear Factor-κB (NF-κB) inflammatory pathway through the G Protein-coupled Receptor 43 (GPR43), and enhance the anti-hepatocellular carcinoma efficacy of APs [24].

Embolic drug delivery systems block blood supply and nutrients to the target area, exerting a dual effect of embolization and chemotherapy. They also belong to physicochemical targeted formulations. To address the limitations of embolic agents in Transarterial Chemoembolization (TACE), Spirulina (SP) has been applied to embolic drug delivery systems for liver cancer. Its algae blue protein with anti-tumor activity, negatively charged surface, and helical structure that can load drugs through electrostatic interaction, and with a particle size of 100–500 μm and mobility, it can achieve vascular embolization to make up for the deficiencies of traditional non-degradable embolic agents [25].

IV. Conclusion

In conclusion, liver cancer has become a major malignant tumor threatening global public health. The current treatment methods are still plagued by problems such as drug resistance, significant adverse reactions, and limited applicability. Active components from natural medicines, with their unique advantages of multi-targeting, multi-pathway regulation, and low toxicity, have shown significant potential in inhibiting liver cancer proliferation, metastasis, and angiogenesis, as well as inducing programmed cell death in liver cancer cells. They provide a new direction for overcoming the bottlenecks in clinical treatment. This review also discusses the prominent advantages of new targeted delivery systems in liver cancer treatment, but current research still has obvious deficiencies: although some natural drug active ingredients are known to have anti-tumor activity, their specific molecular mechanisms, core targets, and regulatory pathways are still unclear, and the association with cell death pathways such as ferroptosis still needs to be further clarified; at the same time, most components have poor water solubility and low bioavailability, and the design of delivery systems and formulations is relatively lagging behind. Therefore, future research should focus on three major directions: first, combine multi-omics technologies such as Transcriptomics (RNA-seq) and proteomics (iTRAQ/TMT) to precisely screen core targets, and combine epigenomics methods such as Chromatin Immunoprecipitation sequencing (ChIP-seq) to clarify the regulatory mechanism of natural drugs; second, develop advanced technologies such as nanodelivery and targeted carriers to improve drug stability and targeting; third, promote collaborative treatment research between natural drugs and targeted drugs, immune drugs, and conduct multi-center clinical trials to strengthen the clinical relevance of mechanisms, avoiding the research gap of "effective in vitro, ineffective in vivo".

Conflict of Interest

The authors declare no conflict of interest.

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