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REVIEW

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Research progress on natural products against hepatocellular carcinoma

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Abstract: Hepatocellular carcinoma (HCC) remains a prevalent and challenging malignancy globally, characterized by its numerous causal factors and generally unfavorable prognosis. In the relentless pursuit of effective treatment modalities, natural products have emerged as a promising and relatively non-toxic alternative, garnering significant interest. The integration of natural products with contemporary medical research has yielded encouraging therapeutic outcomes in the management of HCC. This review offers a comprehensive overview of the causal factors underlying HCC, and the diverse treatment options available, and highlights the advancements made by natural products in anti-HCC research. Particularly, we provide an outline of the various types of natural products, their corresponding nomenclature, target molecules, and mechanisms of action that exhibit anti-HCC activities. Natural products are anticipated to play a pivotal role in future comprehensive treatment plans for liver cancer, potentially offering patients improved survival rates and an enhanced quality of life.

Introduction

Hepatocellular carcinoma (HCC) is a widely prevalent malignant tumor with a worldwide increasing incidence [1]. In 2020, the number of new cases of primary liver cancer exceeded 900,000, resulting in approximately 830,000 deaths [2]. Currently, the incidence rate of HCC in China has begun to stabilize, representing 4.7% of the global incidence, with a mortality rate of 8.3% globally [3]. It is estimated that the number of liver cancer patients worldwide will exceed one million annually by 2025 [4]. HCC is the most common pathological type of primary liver cancer, making its treatment a significant challenge in global healthcare. Due to late-stage diagnosis, the optimal treatment window often passes by the time of diagnosis, and HCC is a highly invasive cancer often accompanied by liver function damage. Advanced HCC patients exhibit a poor prognosis, marked by a significant decrease in survival rates and a high risk of recurrence, often reaching 70% or higher [5]. Therefore, current treatment outcomes for HCC are inadequate, and new treatment strategies are warranted [6].

As early as thousands of years ago, the medicinal uses of natural products such as fungi, plants, and animals have been recorded in ancient prescriptions of human history [7]. Therefore, natural products exhibit great potential in searching for new therapeutic candidate drugs [8]. By combining modern tools such as molecular biology, biochemistry, and chemistry, compounds extracted from natural products can not only be used to treat diseases but also play an important role in drug development. This enables us to better analyze the biological effects and potential interactions of these compounds on the human body [9]. These research advances have made compounds extracted from natural products potential new therapies for many complex diseases, including inflammation, infectious and neurodegenerative diseases, and cancer [10]. Therefore, people began to study various components extracted from natural products and applied them in clinical trials [11].

After achieving success [12], people began to actively explore different plants to find drugs with potential anti-cancer potential [13]. Previous research reports indicate that natural products and compounds extracted from natural products can inhibit cell proliferation [14], inhibit cancer

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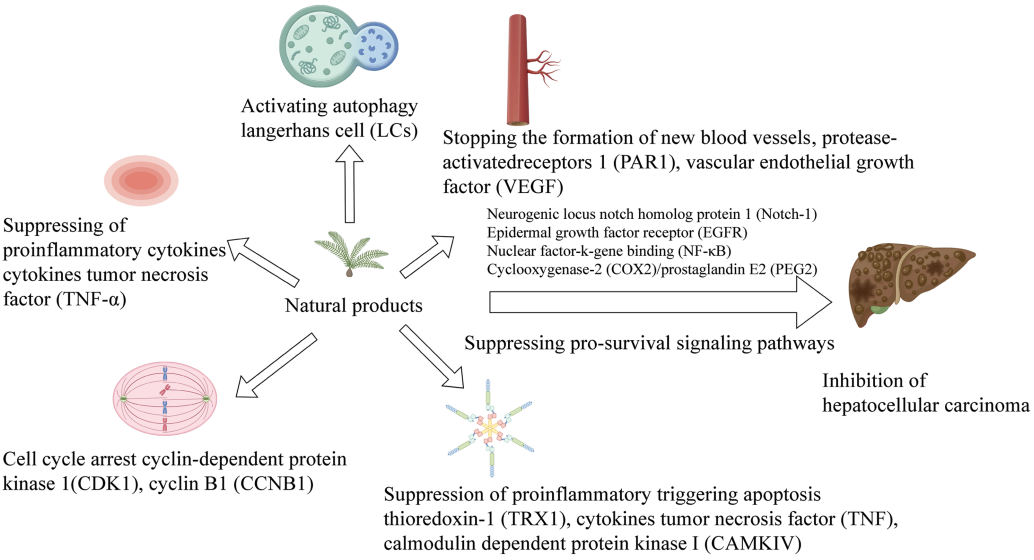

FIGURE 1. Natural product therapy for HCC from different pathways (By Figdraw).

transformation, and effectively prevent tumor metastasis [15]. Through the complex mechanism of traditional Chinese medicine (TCM) preparations with multi-target and multi-component characteristics in network pharmacology [16], new strategies for the treatment of HCC with natural products are provided (Fig. 1).

The comprehensiveness, systematicity, and wholeness of network pharmacology are consistent with the multi-compound, multi-target, and multi-pathway characteristics of natural products [17]. Network pharmacology is to explore the mechanism of TCM in the treatment of HCC by integrating bioinformatics and molecular docking technology. Previous studies revealed that many decoctions may play an anti-HCC role by regulating specific signaling pathways and biological processes [18], which provides a new idea for the treatment of HCC, making traditional Chinese medicine play an important role in anti-cancer research. However, further research is still needed in this field to further understand the potential mechanism of TCM in the treatment of HCC and lay the foundation for individualized treatment and more effective clinical application. To explore the therapeutic potential of natural products, researchers have chosen different protein targets, including apoptotic proteins and transcription factors. This study encompasses the factors that initiate HCC, an examination of its etiology, the present-day treatment modalities available for HCC, and a subsequent assessment of the varying natural product components that can serve as potential therapeutic targets. From the perspective of natural products, we searched for relevant literature generated from various databases for the treatment of HCC. After searching the keywords “natural products” and “hepatocellular carcinoma” OR “HCC”, a total of 5,603 articles were found, of which 2,399 were retrieved from Web of Science, 604 from PubMed, and 2,600 records were retrieved from Scopus. After removing the repeated literature in the database, there were 980 references. After the screening of titles and abstracts, the remaining 612 articles were evaluated, and finally, 59 articles were included in the literature review for analysis. These literature studies finally highlighted the association of HCC and its treatment with natural products, providing a rich literature reference value for the treatment of HCC (Fig. 2).

The Triggering Factors of HCC

The occurrence of HCC is the result of a combination of multiple factors. Liver fibrosis is a pathological process of fibrosis and scarring in liver tissue, usually caused by liver diseases such as chronic hepatitis, alcohol abuse, and fatty liver, which increases the risk of developing HCC. Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the main viral causes, and their long-term infection can lead to chronic hepatitis and cirrhosis, exacerbating the development of HCC. The co-infection of hepatitis D virus (HDV) and HBV also increases the risk of developing HCC. Age and sex are also influencing factors, and males and older individuals are more likely to develop HCC. In addition, liver lesions, genetic factors, environmental factors, and exposure to certain drugs and chemicals may also increase the risk of developing HCC. These factors are often interrelated and together promote the development of HCC [19].

Liver fibrosis

Liver fibrosis is one of the factors that may trigger HCC, and it is also a key factor leading to an increase in mortality in liver disease patients [20]. Individuals with progressive liver fibrosis will eventually develop into liver failure or HCC [21]. When our body develops fatty liver, if not actively controlled or treated, it may lead to liver fibrosis. Because of the fatty liver can lead to excessive accumulation of fat in the liver under different conditions, leading to sustained damage, hepatocyte steatosis, and ultimately evolving into liver fibrosis. In addition, patients with chronic viral hepatitis may also experience varying degrees of liver fibrosis. This is because the virus persists in the body and can cause recurrent or persistent inflammation in the liver, which in the long run will inevitably lead to liver fibrosis. Liver

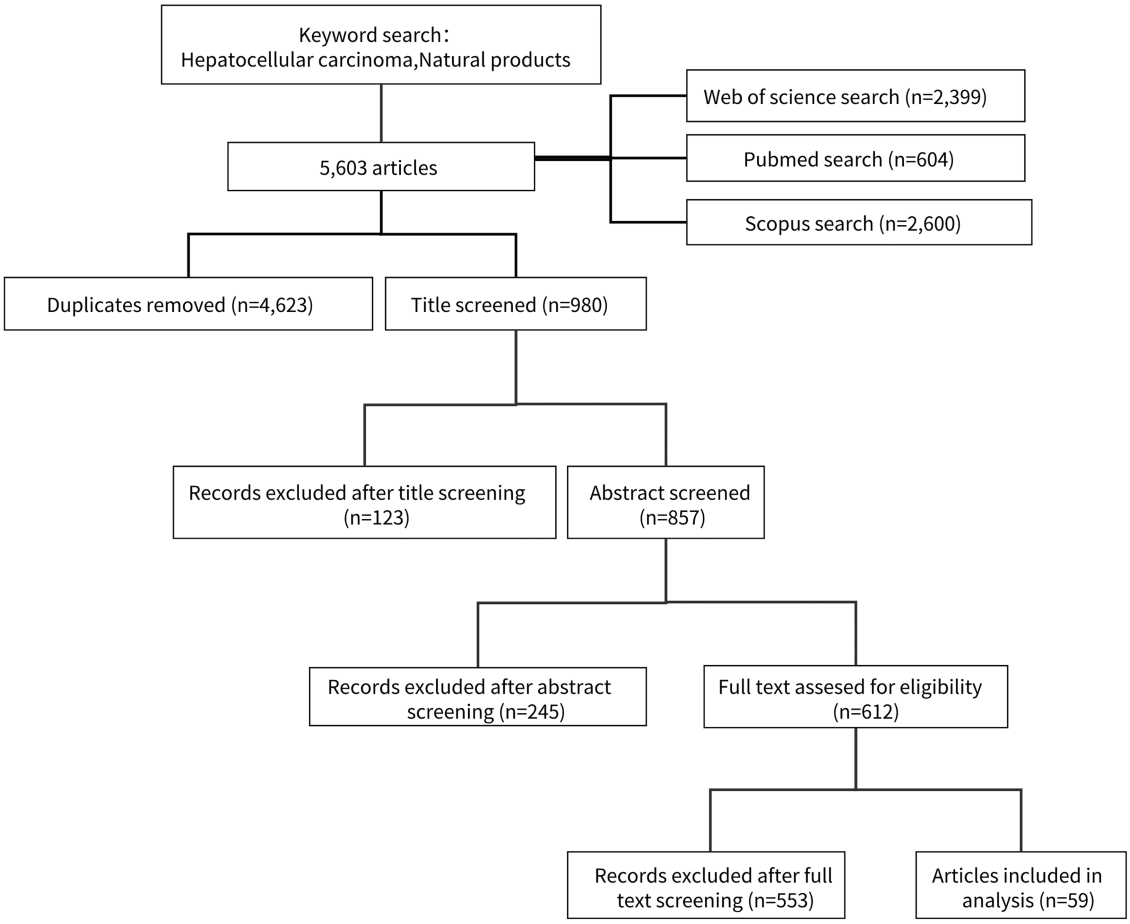

FIGURE 2. The flow chart of the study selection process.

fibrosis can lead to liver failure or HCC, and mesenchymal stromal cells may play a crucial role.

HBV infection

HBV is a DNA virus that can integrate into the host genome, induce insertion mutagenesis, and activate oncogenes [22]. Moreover, HBV infection can inhibit the function of the immune system, which helps to promote the growth and spread of cancer cells, making it more difficult for the body to clear viruses and resist other pathogens. There is a close correlation between HBV infection and HCC. Firstly, HBV infection often leads to chronic hepatitis, which is a long-term and progressive inflammatory process that can damage liver tissue. Persistent hepatitis leads to gradual liver damage, increasing the risk of developing HCC. In addition, inflammation caused by HBV leads to oxidative stress, releasing free radicals, which can damage DNA and other cellular structures. Oxidative stress is related to the development of cancer, as it may lead to DNA mutations, thereby promoting tumor formation. Finally, HBV infection can also trigger secondary infections, which can increase the risk of HCC. According to a survey, 69.9% of Chinese HCC patients have a background of HBV infection, 5.2% have HCV infection, and 5.8% have both HBV and HCV infections [23]. The occurrence of HBV-induced HCC is a complex, multifactorial, and progressive process that involves the interaction between the virus and endogenous mutagens, as well as the host's immune response to the virus [24].

HCV infection

HCV-induced HCC is mainly related to the host's sustained immune response and chronic inflammation caused by acute infection clearance failure, leading to liver fibrosis and cirrhosis, ultimately developing into HCC [25,26]. There is also a close correlation between HCV infection and HCC. Firstly, HCV infection often leads to chronic hepatitis, causing fibrosis of liver tissue and transforming into cirrhosis. At this time, liver tissue becomes scarred, which increases the risk of developing HCC. Unlike HBV, HCV is an RNA virus that is not integrated into the host genome, and its treatment has also been quite successful. Due to the ongoing risk of developing HCC in patients with HCV-induced cirrhosis, we need to constantly monitor [27]. Secondly, HCV may also trigger carcinogenic changes in liver cells, directly promoting the development of HCC. Finally, the combination of alcohol abuse and HCV infection increases the risk of developing HCC.

HDV infection

HDV is an RNA virus that encodes only one type δ Protein or δ Antigen (HDAg) is a virus that requires the presence of HBV for replication and infection [28]. Large hepatitis D antigen (L-HDAg) may activate signal transduction and transcription activating factor 3 (STAT3) or oxidative stress-induced nuclear factor kappa-B (NF-κB) activation to promote inflammation. The effects of this inflammatory response include endoplasmic reticulum stress and

necrotizing inflammation, as well as an increase in reactive oxygen species generation, which may ultimately lead to the occurrence of HCC [29]. Therefore, HDV cannot integrate viral genes into the host genome and must rely on HBV for replication. HDV indirectly causes HCC [30].

HDV is usually co-infected with HBV because it requires HBV to provide coating and other key factors for replication and infection. It means that the patient is carrying both viruses, namely HBV and HDV. This co-infection increases the severity of hepatitis and increases the risk of developing HCC. HDV infection can lead to a more severe course of hepatitis, and patients who are infected with HBV alone are more prone to liver inflammation, liver cell damage, and fibrosis. Persistent liver inflammation occurs, which stimulates liver cell proliferation and increases the risk of cancer. HDV infection is often associated with liver fibrosis and the progression of cirrhosis. Cirrhosis causes significant changes in liver tissue, causing serious damage to liver function, and is also a prerequisite for leading to HCC. According to investigations, the risk of HCC in patients with acute HDV infection (relative risk (RR) 6.1, 95% (confidence interval (CI) 2.8–11.7) or chronic HDV infection (RR 3.9, 95% CI 1.6–7.2) is significantly higher than that in individuals infected with HBV alone [31]. Overall, HDV infection increases the risk of multiple viruses in patients, increases the severity of hepatitis, and leads to persistent inflammation and liver fibrosis, all of which together increase the risk of HCC.

Other factors

Age is an important risk factor for HCC. HCC is more common in middle-aged and elderly people, especially in the 70-year-old population, the age-specific incidence rate reported is the highest [32]. This may be related to long-term exposure to potential carcinogenic factors, such as viral infections or alcohol abuse. In addition, age is also associated with gradual damage and mutations in liver cells, increasing the risk of cancer development. Sex also plays an important role in the pathogenesis of HCC. Generally speaking, men are more likely to suffer from HCC, and its incidence rate is significantly higher than that of women. This may be partly due to men being more exposed to risk factors for liver cancer, such as alcohol abuse and viral infections [33]. Hormonal factors may also play a role in gender differences, although the specific mechanisms are not yet clear. According to the survey, the incidence rate varies with different races. This difference in incidence rate may be partly due to the high incidence rate of single nucleotide variation in patatin-like phospholipase domain containing 3 (PNPLA3), which is related to non-alcoholic steatohepatitis (NASH) related HCC [34]. Smoking can also increase the risk of HCC [35]. Genetic factors may also affect the risk of HCC. If there is a history of HCC in the family, the individual's risk may increase. Certain genetic mutations may increase the genetic predisposition of HCC. The health of the immune system is crucial for preventing the development and spread of cancer cells. Damage or inhibition of the immune system may make cancer more likely to develop. However, the role of diet in regulating the risk of HCC is not yet clear, but studies have shown that coffee and aspirin have preventive effects [36].

Treatment Methods for HCC

With the progress of science and technology, in addition to surgical treatment, immunotherapy, targeted therapy, and interventional therapy, nanotechnology has emerged in recent years to treat hepatocellular carcinoma [37]. With the development of nanotechnology, more and more nanomedicines have been developed and applied in the biomedical field [38]. Through rational design, nanomedicines can be prepared into therapeutic agents with appropriate size, and surface modification specific liver cancer targeting ligands and simultaneously loaded with a variety of different mechanisms of action, to improve the bioavailability of drugs, enhance the targeting of liver cancer, reduce the toxic and side effects on normal tissues, and provide new hope for the treatment of liver cancer. Some receptors are often specifically expressed or overexpressed on the surface of hepatocellular carcinoma. Therefore, when designing nanomedicines, ligand molecules with high affinity for these receptors are coupled on the surface of nanomedicines to connect them with "missile molecules", which can guide the drug delivery to the target site and realize the accumulation of drugs in liver tissues or liver cancer cells [39]. These active targeting ligand molecules include some small molecules, sugars, peptides, antibodies, etc. Under receptor ligand-mediated active targeting, nanomedicines can enter cells through the endocytic pathway, increasing the intracellular drug concentration. To achieve the purpose of treating hepatocellular carcinoma.

Surgical treatment

Surgical treatment is the main method for early HCC. When performing surgical treatment, it is necessary to conduct preoperative evaluation first, including checking the type, size, and location of the tumor, and whether there are signs of metastasis to other organs [40]. The overall health status of patients should also be evaluated to ensure they can withstand surgery. Surgical treatment will determine the type of surgery based on the nature and location of the tumor (Fig. 3A).

For example ① Hepatolobectomy. In this surgery, the doctor will remove a portion of the liver containing the tumor. ② Hepatolobectomy combined with intraoperative cryoresection. For some larger tumors, doctors may use intraoperative cryoresection to preserve healthy liver tissue to the greatest extent possible. ③ Liver transplantation. For some severe cases of HCC, liver transplantation surgery may be necessary, where the entire liver is replaced with a healthy donor liver.

Before surgery, patients need to follow the doctor's advice, including stopping the use of specific medications, fasting, etc. Surgery is usually performed under general anesthesia, where the doctor enters the abdominal cavity through an incision and then removes the tumor or the entire liver according to the condition. After surgery, patients need to receive monitoring and treatment in the

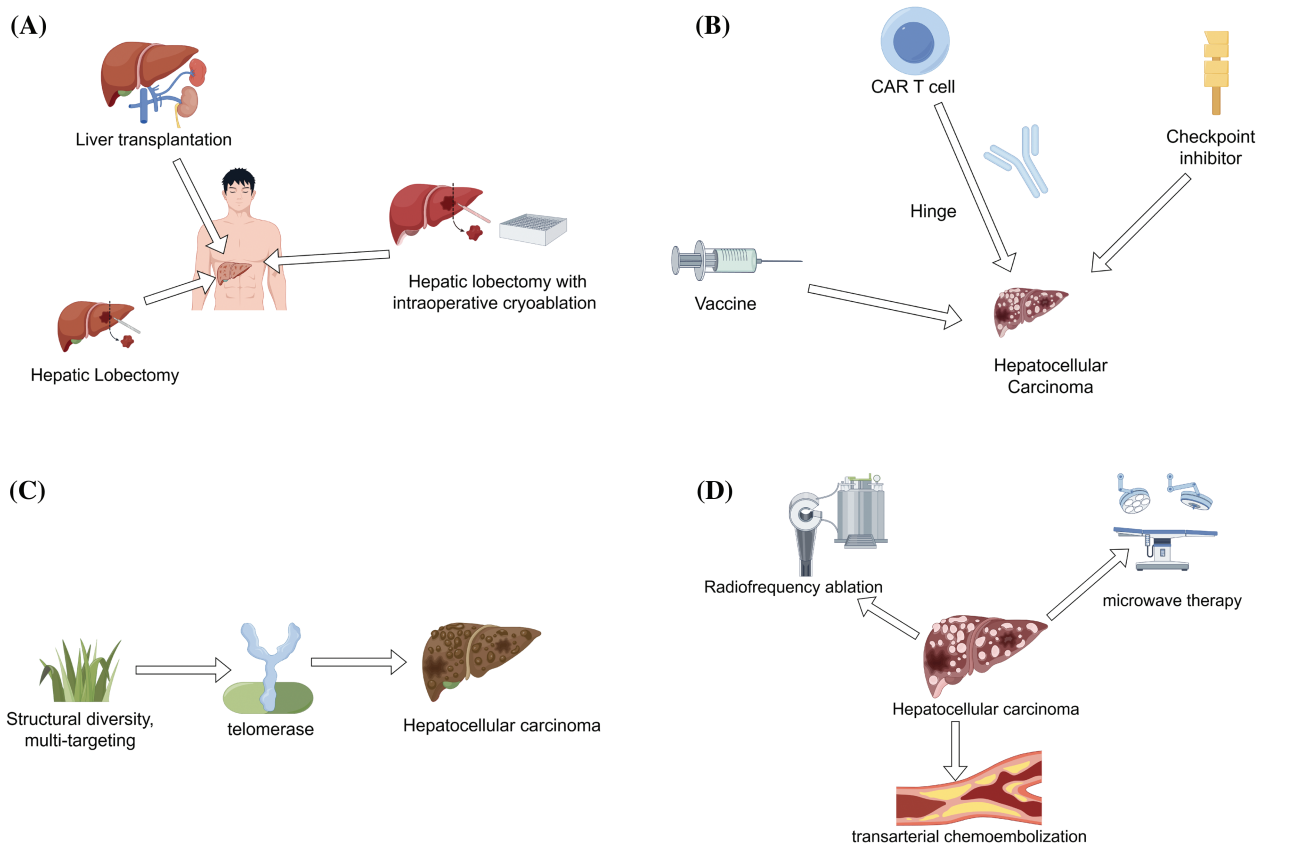

FIGURE 3. Treatment methods of HCC (By Figdraw). (A). Surgical treatment-lobectomy, intraoperative frozen resection, and liver transplantation, (B). Immunotherapy-checkpoint inhibitors, CAR-T cell therapy, and cancer vaccines, (C). Targeted therapy-inhibition of telomerase activity, (D). Interventional therapy-radiofrequency ablation, microwave therapy, and transarterial chemoembolization.

hospital to ensure no complications. Postoperative patients need to undergo regular follow-up and receive chemotherapy, radiation therapy, or other treatments to prevent the recurrence of cancer cells.

Immunotherapy treatment

Immunotherapy is currently a promising method for treating HCC [41]. For example, monocarboxylate transporter (MCT) 4 in HCC is overexpressed, and VB124 (a high-potential MCT4 inhibitor) is used to inhibit MCT. This immunotherapy response targeting MCT4 has been shown to have anti-HCC effects and can produce an immunosuppressive liver cancer environment [42].

Immunotherapy is the process of enhancing or adjusting a patient's immune system to better recognize and attack cancer cells. It includes various methods, such as checkpoint inhibitors, chimeric antigen receptor T cell immunotherapy (CAR-T) cell therapy, cancer vaccines, etc. (Fig. 3B). The common goal of these methods is to combat cancer by activating the immune system, stimulating immune cells and enhancing anti-cancer effects by infusing cytokines, vaccines, and T cells [43]. Immunotherapy is successful and safe in the treatment of HCC, with long-term survival and controllable toxicity [44,45]. One of the earliest immunotherapy methods used for HCC was vaccination. Due to the risk-free nature of vaccination, HepG2 cell lines and autologous tumor lysates have been used in clinical trials [46].

Targeted therapy treatment

Targeted therapy is a new treatment method that can more accurately attack cancer cells, treating cancer by interfering with or blocking specific molecules or signaling pathways associated with cancer. According to the investigation, molecular targeted drugs currently have good effects in Phase III clinical practice and can significantly improve survival rates [47]. Due to the high expression of the angiogenesis promoter vascular endothelial growth factor (VEGF), it leads to vascular proliferation and causes HCC. Therefore, the current molecular-targeted therapy strategies for HCC mainly target VEGF and other angiogenic pathways [48].

Natural products have a wide range of pharmacological effects, with multiple components and targets, playing a crucial role in the treatment of HCC [49]. In recent years, natural products have been a hot topic and research direction in targeted therapies due to their structural diversity, multi-target effects, and minimal toxic side effects [50]. We are actively developing more molecular targeted drugs targeting the important targets that cause HCC. Telomerase is an attractive target for selective cancer treatment as it plays a crucial role in cell immortality. Previous research has shown that Imetelstat (GRN163L) [51], Periposine [52], KML001 [53], and BIBR1532 [54] can inhibit telomerase activity, cause telomere loss, and control cell growth rate to treat HCC (Fig. 3C).

Interventional therapy treatment

Radiofrequency ablation and microwave therapy are two commonly used interventional treatment methods for HCC, both aimed at destroying tumor tissue, but using different energy sources and principles (Fig. 3D). Both of these treatment methods can be used to treat early HCC or as adjuvant therapy to alleviate symptoms in patients. Radiofrequency ablation is a method of destroying liver cancer cells using the thermal energy generated by high-frequency currents. This process is usually completed by introducing radiofrequency electrodes directly into the interior of the tumor. Electrodes generate high temperatures, leading to thermal necrosis of surrounding tissues, which has a killing effect on tumor tissue. Radiofrequency ablation is commonly used for small, localized liver cancer lesions, especially in patients who are not suitable for surgical resection, such as due to liver dysfunction or other health reasons. This method is usually minimally invasive and recovers quickly but may require multiple treatments to ensure complete removal of the tumor.

Microwave therapy is also a method of destroying HCC by generating heat energy through high-frequency microwaves, but unlike radiofrequency ablation, it uses microwave energy instead of electric current. Microwave energy is directly directed into the interior of the tumor by introducing microwave antennas, generating high temperatures to destroy tumor tissue. Microwave therapy may be faster and more effective in certain situations, especially for large tumors or tumors at risk. Like radiofrequency ablation, microwave therapy is usually minimally invasive and helps reduce postoperative recovery time for patients.

Transcatheter arterial chemoembolization (TACE) is also an interventional treatment method for HCC. HCC is usually primary liver cancer, and the main goal of TACE is to slow down or inhibit the growth of HCC and improve the survival rate of patients. The principle of TACE combines two treatment methods, namely chemotherapy and embolization therapy. Chemotherapy: during TACE, anticancer drugs are delivered to the hepatic artery and directly act on the tumor, slowing down or inhibiting cancer growth [55]. Embolism therapy: in addition to drugs, TACE also includes embolic agents, which block the blood supply arteries of tumors, restrict blood flow supply, and thus allow drugs to stay inside the tumor and enhance its therapeutic effect [56]. During the treatment process, TACE is usually performed in the operating room or radiation therapy room by experienced interventional radiologists. Patients may require local anesthesia or sedatives but generally do not require general anesthesia. The doctor introduces a catheter into the hepatic artery system through arterial catheterization to accurately deliver drugs and embolic agents to the area where the tumor is located. The combination of drugs and embolic agents can lead to insufficient blood supply to tumors and drug effects, thereby achieving therapeutic effects. After surgery, the catheter will be removed, and patients need to be observed in the hospital for some time to ensure there are no serious complications.

The advantage of TACE treatment is that it can effectively slow down the growth of HCC, alleviate symptoms, and improve the survival rate. However, TACE typically requires multiple treatments as HCC is a recurrent cancer and may not be a permanent solution for some patients. The frequency and duration of treatment will vary depending on the nature of the tumor and the patient's response.

Research on Natural Products against HCC

Although some progress has been made in the treatment and prevention of HCC, the overall survival rate of HCC patients remains low due to their susceptibility to recurrence and metastasis. In terms of surgical treatment, although the tumor can be completely removed to achieve a curative effect, and for early liver cancer, the cure rate after surgical resection is relatively high. However, for mid to late-stage liver cancer, the surgical risk is high, and the postoperative recurrence rate is high. Some patients cannot afford surgery due to poor physical condition. Immunotherapy can activate the patient's immune system, improve their resistance to tumors, and have a broad-spectrum killing effect, which can reduce tumor recurrence and metastasis. Compared with other treatment methods, the side effects of immunotherapy are relatively small. However, the efficacy of immunotherapy varies from person to person, and some patients may not benefit from it. And immunotherapy needs to be combined with other treatment methods, such as surgery, radiotherapy, etc., to improve the treatment effect. In terms of targeted therapy, it inhibits or disrupts specific receptors or signaling pathways on the surface of tumor cells, with high specificity. Targeted therapy has a relatively small impact on normal cells, reducing the toxic side effects of traditional chemotherapy drugs. It can also target multiple targets and achieve therapeutic effects through multiple pathways and stages. However, targeted therapy requires genetic testing of the patient's tumor to determine the presence of relevant mutated genes, which requires a certain amount of time and cost. Moreover, the long-term efficacy of targeted therapy still needs further observation and research, and some patients may experience drug resistance. Interventional therapy, which is a common approach for treating HCC, mainly treats local tumor lesions without surgery. It is suitable for patients with advanced liver cancer who cannot be operated on, have minimal side effects, and can be treated with embolization. However, the operation is difficult and prone to recurrence after treatment [57]. Both chemical and surgical treatment of interventional therapy could not provide a good prognosis. Therefore, there is an urgency to find an effective way (natural products) to treat HCC [58].

Due to the presence of multiple active ingredients and minimal side effects in natural products, TCM has been found to have good therapeutic effects in the treatment of cancer, such as choriocarcinoma, esophageal cancer, leukemia, and nasopharyngeal carcinoma, according to traditional folk therapies [59]. The evidence-based function of Chinese herbal medicine in anti-cancer is to prevent tumor growth and metastasis, as well as to alleviate the side effects or complications of treatment strategies such as chemotherapy, radiotherapy, and resection [60]. A large

number of studies have adopted molecular docking techniques to explore the binding ability of key active ingredients and targets in natural products, to improve the prognosis of HCC patients after resection surgery [61]. An increasing number of studies indicate that natural products have enormous potential in developing alternative anti-cancer drugs [62]. Natural products have the characteristics of multiple compounds, targets, and pathways when applied in disease prevention and treatment. Molecular docking technology can simulate the results of drug-target interactions [63], making it easier to screen for anticancer drugs. At present, flavonoids [64–66], alkaloids, phenolic alcohols [67], and other TCM extracts in natural products have been found to exhibit strong anti-cancer activity in HCC treatment.

Flavonoids

It was revealed that flavonoids have benefits in inhibiting the occurrence and development of cancer [68,69], and play a crucial role in the chemoprevention of HCC [70]. Flavonoids have anti-thrombotic, antioxidant, hepatoprotective, and anti-inflammatory properties [71], and have a wide range of pharmacological effects in TCM [72]. Flavonoids extracted from natural products have been proven to have neuroprotective effects, myocardial injury protective effects, alleviating liver steatosis, and inducing apoptosis in human epithelial ovarian cancer cell SK-OV-3 [73–76], exhibiting anticancer activity. Moreover, flavonoids can also treat chronic venous insufficiency (CVI) and improve capillary function and have been successfully proven to be safe and effective in elderly patients and pregnant women, with no reported side effects [77]. Flavonoids in some natural products can be applied to daily beverages, and daily consumption can better prevent anti-inflammatory, antioxidant, antimicrobial, antiviral, and hypoglycemic effects [78]. Flavonoids not only exhibit partial anti-cancer and cancer prevention effects, reducing liver damage [79–81] but are also used as liver detoxifiers, possibly inhibiting the survival and angiogenesis of liver cancer cells [82]. We have summarized different kinds of flavonoids that may be used for the treatment of HCC, including their names, sources, targets, and mechanisms of action (Table 1).

TABLE 1

Flavonoid compounds against HCC

Compound name	Source	Targets	Mechanism of action	References
Isoquercitrin	*Ginkgo biloba* L.	Cyclin-Dependent Kinase 6 (CDK6)	Isoquercitrin has been confirmed as a potential splicing inhibitor [83,84]. It exhibits anti-cancer effects against HepG2 and Huh7 HCC cells by downregulating CDK6 [85,86].	[87]
Tiliroside	*Crataegus pinnatifida* (hawthorn)	TANK-binding kinase 1 (TBK1), Epichlorohydrin (ECH)	Tiliroside can be used as a drug for HCC by downregulated p62 protein and upregulated ECH-associated proteins.	[88]
Calycosin-7-glucoside	*Astragalus membranaceus var. membranaceus*	Thioredoxin 1 (TRX1)	It inhibits HCC proliferation, promotes apoptosis, regulates oxidative stress, and modulates TRX1 expression.	[89]
Baicalin	*Astragalus membranaceus var. membranaceus*	Rho-associated protein kinase 1 (ROCK1)	Baicalin inhibits ROCK1/GSK-3β/β-catenin signaling pathway to reduce the proliferation and metastasis of HCC.	[90]
Calycosin	*Astragalus membranaceus var. membranaceus*	Interferon-gamma (IFN-γ) Caspase 3/9 (CASP 3/9)	Baicalein showed a significant antiproliferative effect on HepG2 cells by activating the caspase-3/9 pathway.	[91]
Myricetin	*Myrica rubra* (bayberry)	Protease-Activated Receptor 1 (PAR1)	Myricetin reverses PAR1-mediated EET by targeting PAR1 and inhibits HCC cell invasion and metastasis.	[92]
(5,7,8,4′-tetrahydroxyflavone)-3′-4-(5,7-dihydroxyflavone) (Japoflavone D, JFD)	*Lonicera japonica* (honeysuckle)	Extracellular Signal-Regulated Kinase/Mammalian Target of Rapamycin (ERK/mTOR), Kelch-like ECH-Associated Protein 1/Nuclear Factor Erythroid 2-Related Factor 2 (Keap1/Nrf2)	JFD inhibited the activation of ERK and mTOR and activated the Keap1/Nrf2 signaling axis.	[93]

(Continued)

Table 1 (continued)

Compound name	Source	Targets	Mechanism of action	References
Troxerutin (TX)	Sophora japonica var. japonica	Nuclear Factor-κB (NF-κB)	TX inhibits IKKβ expression, thereby suppressing NF-κB (p65 subunit) nuclear translocation, downregulating NF-κB-mediated inflammation, proliferation, and cell survival.	[94]
Quercetin	*Styphnolobium japonicum* (L.) *Schott*	Hexokinase 2 (HK2), Protein Kinase B/Mammalian Target of Rapamycin (AKT/mTOR)	Quercetin lowers HK2 protein levels and inhibits the AKT/mTOR pathway in HCC cells to suppress HCC development.	[95]
Wogonin	*Scutellaria baicalensis* (skullcap)	Glycogen Synthase Kinase 3 beta (GSK3β) and Cyclin D1	Wogonin inhibits *in vivo* hepatic tumor growth by phosphorylating GSK3β and Cyclin D1.	[96]
Oligomeric proanthocyanidin B2 (OPC-B2)	*Arachis hypogaea* L.	Protein Kinase B (Akt)	OPC-B2 significantly inhibits HCC cell proliferation, and tumor growth and inhibits Akt activity *in vitro* and *in vivo*.	[97]

Alkaloids

In folk therapies, alkaloids extracted from natural products exhibit an excellent effect on inhibiting cancer by inhibiting cell division, inducing apoptosis, and inhibiting angiogenesis, thereby inhibiting the activity of cancer cells [98,99]. Alkaloid compounds can inhibit the growth of HCC by inducing cell aging and cell cycle arrest, as cell aging is an irreversible state of cell cycle arrest, in which senescent cells permanently lose their proliferative ability [100]. Currently, inducing cell aging to slow down cancer cell proliferation is also a powerful defense against cancer (Table 2).

TABLE 2

Alkaloid compounds against HCC

Compound name	Source	Targets	Mechanism of action	References
Stachydrine hydrochloride (SH)	*Panzerina lanata var. alaschanica (Kuprian.) H. W. Li*	Leukemia Inhibitory Factor (LIF), Phosphorylated AMP-activated Protein Kinase (p-AMPK)	SH retards the proliferation of HCC cells by downregulating the expression of LIF and upregulating p-AMPK proteins.	[98]
Solanine	*Styphnolobium japonicum* (L.) *Schott*	Tumor Necrosis Factor (TNF), B-cell lymphoma/leukemia-2 (Bcl-2), Bcl-2-associated X protein (Bax)	Modulating TNF expression downregulates Bcl-2 and Bax expressions, reduces the Bcl-2/Bax ratio, obstructs mitochondrial and lysosomal membrane proteins, and activates the caspase cascade to induce cell apoptosis.	[95]
Celastrol	*Tripterygium wilfordii Hook. f.*	Cyclin-Dependent Kinase 1 (CDK1), Cyclin B1 (CCNB1)	Bufotalin inhibits the proliferation of HepG2 and Hep3B cells, decreases CDK1 and CCNB1 expression levels, and suppresses the proliferation of HCC stem cells.	[101]

Phenolic alcohols

It was reported that phenolic compounds have benefits in inhibiting the occurrence and development of cancer, exhibiting not only significant anti-tumor, antioxidant, and anti-inflammatory effects [102–104] but also anti-cancer and anti-inflammatory effects [105]. Previous studies have confirmed that phenolic compounds can induce tumor cell apoptosis, arrest cell cycle, and autophagy, and therefore may also apply to liver cancer cells [106–108]. In TCM prescriptions, according to surveys, phenolic compounds are the basic components for treating various diseases (such as blood stasis, pain relief, etc.) [109], and have far-reaching therapeutic effects on tumors [110], which can reduce inflammation [111] and protect the liver [112–114]. At present, bioactive extracts have been extracted from natural products of TCM to combat HCC [115], mainly by inducing cell apoptosis, regulating inflammatory response, and increasing the expression of HCC-specific proteins (Table 3).

TABLE 3

Phenolic-alcohol compounds against HCC

Compound name	Source	Targets	Mechanism of action	References
Kaempferol	*Lonicera japonica* var.	Bax, CDK1	Kaempferol promotes the expression of Bcl-2-associated X protein (BAX) and Jun proto-oncogene (JUN) proteins and inhibits the expression of CDK1 protein.	[116]
MOF extract	*Moringa oleifera Lam.*	Caspase-3 (CASP3)	The MOF extract inhibits the growth of HepG3 cells by upregulating the expression of caspase-3 protein.	[117]
Hesperidin	*Citrus* L.	Bax, CASP3	Hesperidin significantly reduces the proliferation of HepG2 and SH-SY5Y cells and induces cell apoptosis through upregulating pro-apoptotic Bax protein activating caspase-3 dependent intrinsic pathway.	[118]
Curcumin	*Curcuma longa* L.	Vascular Endothelial Growth Factor A (VEGFA)	By inducing cell apoptosis, regulating inflammatory responses, and increasing the expression of VEGFA protein.	[119]

Other types of compounds

Apart from the compounds enumerated in the aforementioned categories, there exist extracts derived from certain natural products, which possess the capability of addressing HCC. The derivative compounds isolated from natural product extracts have been proven to inhibit the growth of HCC and induce cell apoptosis [120]. In TCM formulas, there are medicinal herbs specifically used to treat diseases related to the liver meridian and related organs, which have bioactive ingredients against HCC [121] and can effectively eliminate 'liver fire'. They have been confirmed in liver diseases such as HCC [122], non-alcoholic fatty liver [123], and liver failure [124]. Extracts of other natural products can also reduce the activity of HCC cells [125], inhibit proliferation [126], prevent migration [127] and invasion [128], and induce cell apoptosis [129]. They have physiological activities such as anti-tumor [130], liver protection [131], immune regulation [132], inhibition of neointimal formation [133], lowering blood pressure and cholesterol [134], and inhibition of platelet aggregation [135]. They can also promote angiogenesis and endothelial cell proliferation or growth, which exhibits growth inhibition and induces cell apoptosis [136] (Table 4).

TABLE 4

Other types of compounds against HCC

Compound name	Source	Targets	Mechanism of action	References
Coumarin derivatives	*Cnidium monnieri* (L.) *Cuss.*	Epidermal Growth Factor Receptor (EGFR), Rapidly Accelerated Fibrosarcoma (RAF), Platelet-Derived Growth Factor Receptor (PDGFR)	By downregulating the expression of RAF, EGFR, and PDGFR proteins.	[17]
Taraxacum mongolicum	*Taraxacum mongolicum Hand.-Mazz.*	Heat Shock Protein 90 Alpha Family Class A Member 1 (HSP90AA1), Heat Shock Protein 90 (HSP90)	It inhibits the proliferation of HCC cells by up-regulating HSP90 protein and down-regulating HSP90AA1 gene expression.	[137]
Antrodia cinnamomea	*Antrodia cinnamomea (Taiwanofungus)*	Phosphoinositide 3-kinase (PI3K)/AKT	Reduces PI3K/AKT signaling, and downregulates cell cycle-related proteins, aiding in HCC growth suppression.	[138]
Seco-glucoside and isochlorogenic acid	*Cichorium intybus* L. seeds	Tumor protein p53 (p53)	Compounds upregulating the expression of p53 protein.	[139]
Poria cocos polysaccharide	*Poria cocos (Schw.) Wolf*	ALB, VEGFA	Clinical HCC samples show reduced ALB expression, increased VEGFA content, induced cell death, enhanced immunity, and modified tumor microenvironment.	[140]

Discussion

The liver is a critical organ in the human body. Primarily, it serves as a metabolic hub, participating in the breakdown and synthesis of essential nutrients such as carbohydrates, lipids, and proteins. This helps to maintain blood sugar levels and stores energy for later use. Additionally, the liver has a robust detoxification capacity. It efficiently purifies the blood, ridding the body of harmful substances, including those produced during metabolism and environmental toxins [141]. By converting these substances into harmless metabolites, the liver effectively removes them from the body [142]. Furthermore, the liver plays a crucial role in lipid metabolism. It synthesizes and regulates cholesterol levels, ensuring a balanced lipid profile in the body. A key function of the liver is secreting bile, which assists in the digestion of fats. The liver is also responsible for producing various proteins essential for bodily functions. These include plasma proteins, coagulation factors, and hormones. Importantly, the liver serves as a nutrient storage depot. It stores glycogen, the stored form of glucose, and vitamins to meet bodily demands. Additionally, it synthesizes coagulation factors, which control blood clotting and hemostasis [143]. Dysfunction of the liver can lead to bleeding issues and obesity, while obesity increases the risk of developing HCC [144]. Lastly, the liver boosts immune function, assisting the body in defending against infections and diseases. Therefore, it is imperative to prioritize liver health, particularly regarding HCC, and pursue early detection and treatment methods [145].

At present, HCC is of great concern in the medical field, mainly because it is one of the most common cancers worldwide, especially in Asia and Africa [146]. Its high incidence and mortality rate drive the medical community to seek more effective treatment methods [147]. Although the incidence rate and mortality of HCC in China are stable, the limitations of traditional therapies have prompted the medical community to constantly explore new therapeutic strategies such as immunotherapy, targeted therapy, and natural products [148]. Technological progress has also provided more accurate diagnostic and treatment methods, bringing hope for early detection and personalized treatment of HCC. Therefore, HCC, as a difficult cancer to treat, has always been one of the focuses of research and attention in the medical community.

The treatment options for HCC are still relatively limited. Although liver transplantation [149] and surgical resection [150] are considered one of the best treatment options and can improve patient survival [151], there are still many patients who have not adapted to these treatment methods or have drug resistance issues. Due to the significant drawback of high drug resistance in HCC, there is currently no small molecule or antibody therapy that can completely cure HCC. Methods such as liver transplantation and surgical resection only lead to a moderate overall increase in patient survival [152], which is in stark contrast to many other cancers. Even with some approved systemic therapies and surgical options, there is no universal treatment plan applicable to all patients with HCC [153]. The differences in disease conditions, tumor characteristics, and individual reactions among different patients still pose challenges to personalized and precise treatment. Some therapies may be effective in the early stages, but there may be issues with tolerance or reduced efficacy in long-term treatment, which limits the sustainability and effectiveness of the treatment. Although there are many exciting emerging treatment strategies, such as molecular targeted drugs and immunotherapy, many are still in the clinical trial stage and require more research to prove their safety and effectiveness, gradually applied to clinical treatment of HCC patients, and then widely promoted.

At present, the forefront of treating HCC lies in the emergence of immunotherapy and new drugs. Systemic drug treatments such as cabozantinib [154], ramucirumab [155], and immune checkpoint inhibitors [156] significantly improve patient prognosis. The progress of systemic therapy has also attracted attention, and new drugs have shown potential in the treatment of advanced HCC. Although systematic treatment plans have been promoted, their efficacy and survival time are still limited [157]. Natural products possess various beneficial characteristics, including multi-target, multi-level treatment, safety, and bioavailability advantages [158]. The ancient classic work “Compendium of Materia Medica” records the use of various natural products for the treatment of liver cancer. Some of these herbs, such as *Astragalus membranaceus*, *Radix liquidities*, *Angelica Sinensis*, etc., are described as exhibiting the effects of regulating ‘qi’ and blood, tonifying the spleen and kidneys, and enhancing the human immune system, which is helpful in the adjuvant treatment of HCC [159]. ‘Qi’ is an invisible energy phenomenon that exists in every living or inanimate object in the universe, constituting the human body and maintaining its life activities. It is an extremely delicate material, which embodies the unity of important substances and physiological functions in life [160]. In addition, Mulberry leaves, Gardenia, Hawthorn, etc., are also considered to exhibit the effects of clearing heat and detoxifying, promoting blood circulation and removing blood stasis, and can be used to assist in regulating liver function [161]. These ancient works record various herbs and their effects, providing a traditional foundation and direction for the treatment of HCC with TCM. However, further optimization is needed to improve the bioavailability of natural products, reduce nontargeted effects, and maintain therapeutic efficacy. The current challenge is to fully explore the efficacy of natural products, enhance their efficacy against HCC, and reduce nontargeted side effects. Although natural products provide new possibilities for the treatment of HCC, more research and technological optimization are still needed in clinical applications.

In the past decade of research, significant therapeutic effects have been associated with the use of natural products, indicating that innovative development of natural products poses challenges for the treatment of HCC. Starting from the direction of natural products, searching for targets for HCC can better cure the survival rate and

reduce the recurrence rate of HCC patients. Compared with chemically synthesized drugs, these natural products have higher selectivity, can kill liver cancer, and have lower toxicity to healthy cells, making them attractive alternatives for cancer treatment [120]. Therefore, researchers are exploring the components extracted from natural products and these natural products themselves to block specific pathways of cancer formation, which is one of the common strategies for developing anti-cancer drugs [162].

Natural plant products have shown extensive potential for application in the treatment of HCC [163]. Researchers have conducted in-depth research on the mechanisms of action of various natural products in the treatment of HCC. Previous studies have shown that natural plant products, such as flavonoids [68,69], have significant inhibitory effects on liver cancer cells. Flavonoids exhibit multiple mechanisms in the treatment of HCC. They may interfere with the growth and spread of HCC through a variety of pathways, including the regulation of cyclins and apoptosis-related pathways. Especially the intervention of PI3K/Akt and Wnt/β-catenin transduction pathways of factors such as catenin, and inhibition of tumor angiogenesis. This multiple effect makes flavonoids a potential anti-liver cancer drug. Similarly, alkaloid compounds also exhibit multiple mechanisms of action in the treatment of HCC [98]. They play a crucial role in regulating cancer cell proliferation and growth, including inducing apoptosis, blocking the cell cycle, inhibiting angiogenesis, and intervening in tumor metastasis. These compounds may regulate key signaling pathways such as PI3K/Akt, MAPK, NF-κB, etc. [164,165], which affect the survival and proliferation of tumor cells, and inhibit their invasiveness, thereby limiting the growth and spread of tumors. Phenolic compounds also exhibit multiple mechanisms of action in the treatment of HCC. They have strong antioxidant properties, which can inhibit the proliferation of tumor cells, promote apoptosis, and block the invasion and metastasis of tumor cells. These compounds exert their effects by regulating key pathways such as cell cycle, apoptotic signaling pathways, and tumor angiogenesis [166]. In addition, they also affect the tumor microenvironment, reduce the invasiveness and angiogenesis of cancer cells, and limit the growth and spread of tumors. Phenolic alcohol compounds have become potential anti-HCC drugs due to their multiple mechanisms of action [102–104]. These products may exert therapeutic effects by regulating the cell cycle, inducing apoptosis, inhibiting metastasis, and angiogenesis. However, the clinical application of flavonoids in the treatment of HCC is more, the curative effect is better, and the side effects are less [167]. Previous studies have shown that flavonoids have the effects of antioxidation, improving blood circulation, protecting liver activity and multiple mechanisms of action, and helping to reduce the risk of hepatocellular carcinoma [79–81]. With the progress of science and technology, the development of the times, and the update of research methods, flavonoids will have breakthroughs and new understanding in the treatment of human diseases, especially HCC, and will have great practical significance in promoting the development of human health.

Natural products play a crucial role in preventing the development of HCC, partly because they can target specific receptors or regulate immune responses. Some natural products can interact with specific receptors to block the growth and spread of HCC. These products may bind to receptors on the surface of tumor cells, interfere with signaling pathways, and thus limit the proliferation and survival of tumor cells [165]. On the other hand, natural products may also combat HCC by regulating the immune response. They may activate or enhance the immune system, making it more effective in identifying and clearing tumor cells. This immune regulatory effect may include multiple mechanisms, such as enhancing T cell-mediated toxicity, promoting natural killer cell activity, and regulating immunosuppressive factors in the tumor microenvironment [168]. These mechanisms of action indicate that natural products have potential therapeutic value in inhibiting the development of HCC and have become important candidate drugs for studying immunotherapy and targeted therapy.

The application of natural products in inhibiting the development of HCC is not limited to drug therapy but also extends to surgical and interventional treatments. Natural products are widely used in the treatment process before and after surgery, helping to reduce surgical risk, reduce postoperative complications [169], and promote tissue repair [40]. In addition, natural products exhibit unique value in interventional therapy, such as serving as sensitizers or adjunctive therapy drugs during interventional radiation therapy, which helps to improve treatment efficacy and reduce side effects [170]. This comprehensive treatment model uses natural products as supplements or adjuncts to comprehensively apply in the overall treatment strategy of HCC, to achieve better treatment effects and improve patient survival rate.

In searching for treatment options for patients with HCC, we utilize targeted therapy to identify potential natural product drug candidates. The goal is to precisely target the genes associated with HCC, characterize ligand-target protein interactions, and validate the selected ligand as a potential drug candidate [170]. This approach offers an efficient means of screening target genes in HCC research, leveraging the benefits of time-savings and selective treatment with precise targeting of HCC. Although natural products have shown potential value in the treatment of HCC [171], more clinical trials are still needed to verify their safety and efficacy. These substances are expected to be used as independent therapies or in combination with traditional treatment methods, opening up new avenues for the future treatment of HCC. Looking ahead to the future, natural products may complement existing treatment models by combining chemotherapy, radiation therapy, and surgical treatment to improve treatment efficacy, reduce adverse reactions, and slow down tumor resistance [172]. With this comprehensive treatment strategy, natural products are expected to become an indispensable component of future comprehensive treatment plans for

HCC, providing patients with higher survival rates and quality of life.

Conclusion

HCC is not only one of the most common malignant tumors in the world but also has a high mortality and recurrence rate. Due to the complex pathogenesis of hepatocellular carcinoma, the lack of predictable biomarkers, and the problem of persistent drug resistance, these factors have brought limitations to the treatment and continuous treatment. The clinical symptoms of early HCC are not obvious, and 50% of HCC patients are in the advanced stage at the time of diagnosis, and surgical treatment is recommended for advanced HCC. With the development of targeted therapy, the surgical treatment of advanced HCC has made some progress, but the survival benefit of HCC patients is still small, and there are still many limitations and challenges, for example, more than 2/3 of patients still have poor response to immunotherapy [173]. In the clinical practice of immunotherapy, due to the lack of T cells recognizing tumor-specific antigens in patients, some patients are still unable to eliminate tumors by relying on their T cells after the application of Immune checkpoint inhibitors (ICI) based immunotherapy [174]. At present, the pathogenesis of HCC is complex, and a single biomarker cannot accurately predict the prognosis of immunotherapy in HCC patients. Therefore, it is necessary to further explore the research of natural products in hepatocellular carcinoma, and then combine them with nanotechnology to deliver nanodrugs to the tumor site to achieve the accumulation in the tumor site, to achieve the purpose of anti-hepatocellular carcinoma.

Because of the difficulties in the diagnosis and treatment of HCC, the prospect of using natural products and molecular docking technology to develop therapeutic methods is promising and compelling. Compared with synthetic drugs, natural products have a wide variety and low toxicity, and are one of the reliable drug sources [175]. Natural products and their extracts, as anticancer agents, have been reported as natural triggers of apoptosis signaling in different cancers [176] and are effective against a variety of cancer characteristics. We are studying the combination of new technologies such as molecular docking with anticancer drugs. Molecular targeted drugs can regulate autophagy and cell cycle arrest, induce cell senescence, inhibit the occurrence and development of tumors, and play an anti-HCC role. After investigation, it was found that there are a large number of natural products with anticancer properties in nature. Although some of these drugs have been developed and achieved some effects in the treatment of HCC, there are still many unknown natural products that need further research and development. This exploration aims to find a new direction for the treatment of HCC.

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