

# How Traditional Chinese Medicine Works: Biological Mechanisms and Clinical Evidence for Hepatocellular Carcinoma Treatment

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**Abstract:** Hepatocellular carcinoma (HCC) is a malignant tumor with a high mortality rate globally, ranking among the top cancers in incidence and posing a serious human health threat. In recent years, with research advancement in traditional medicine, traditional Chinese medicine (TCM) has attracted increasing interest for its potential role in the management of hepatocellular carcinoma (HCC). As a comprehensive review, this article critically synthesizes the biological mechanisms and clinical application evidence of TCM extracts and classic formulas in HCC treatment, systematically detailing the important roles and specific mechanisms of TCM in inhibiting tumor growth, inducing apoptosis, enhancing immunity, and suppressing angiogenesis. This review aims to synthesize and analyze existing findings to provide a consolidated theoretical basis and identify potential research gaps. Furthermore, it seeks to explore new therapeutic concepts by bridging TCM theory with modern pharmacological approaches, thereby promoting the development of integrated strategies in oncology. Ultimately, we aim to contribute to the improvement of patient survival rates and quality of life. However, while preclinical evidence is promising, the clinical evidence base requires further strengthening through larger-scale, rigorously designed trials to validate efficacy and establish standardized protocols.

**Keywords:** traditional Chinese medicine, liver cancer, formulas, biological mechanisms, clinical evidence

## Introduction

Hepatocellular carcinoma (HCC) refers to malignant tumors that occur in the liver, which can be classified into primary and secondary liver cancers.<sup>1</sup> Primary liver cancer is formed by liver cell transformation, with HCC being the most prevalent type, accounting for approximately 75–85% of primary liver cancer. Other types include cholangiocarcinoma and mixed HCC.<sup>2</sup> Secondary liver cancer, also known as liver metastasis, refers to the transfer of malignant tumor cells from other body parts to the liver through the blood, lymph, and other pathways. Cancers, such as colorectal, gastric, and breast cancer, can all metastasize to the liver.

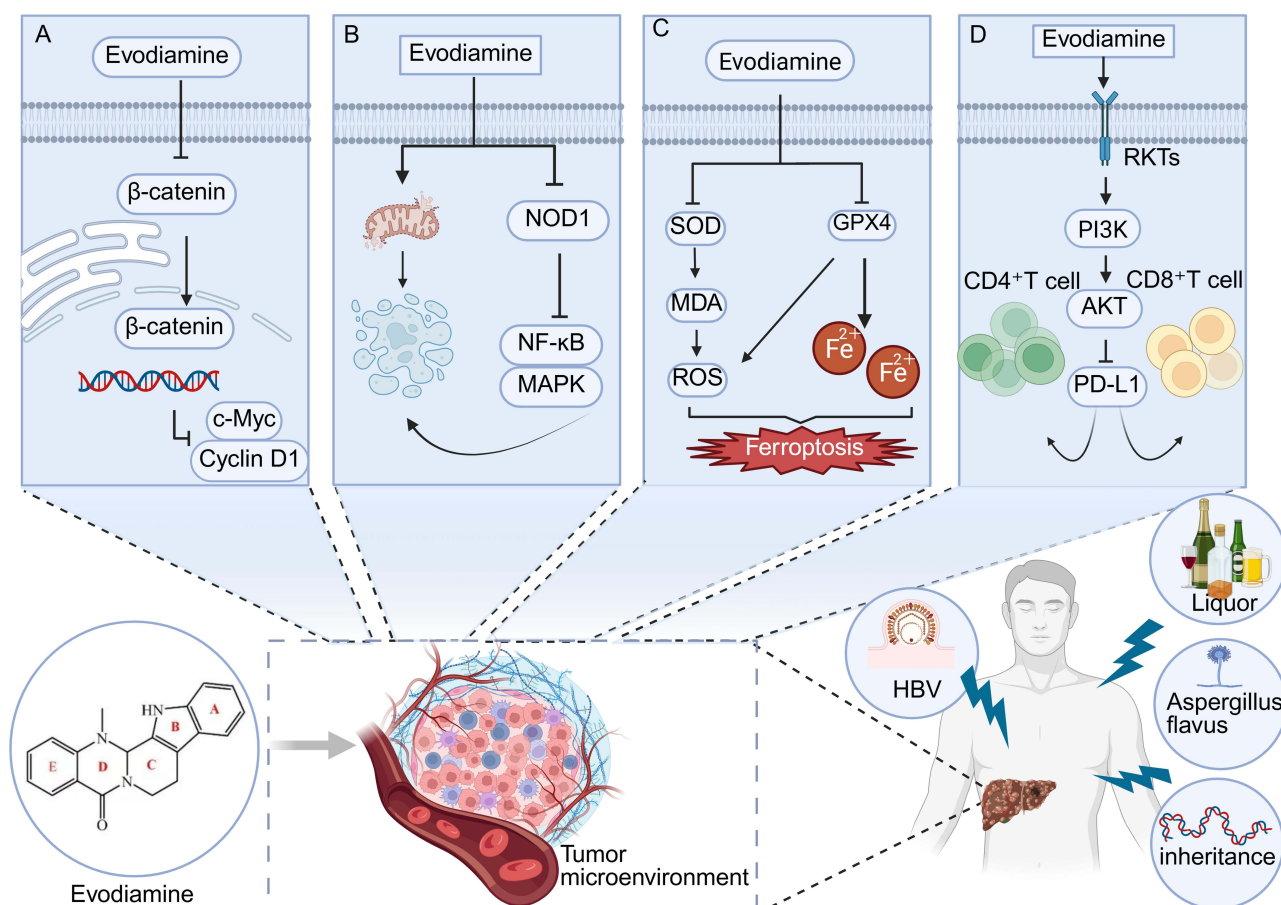
Liver cancer development is a complex process affected by multiple factors and stages. It is primarily associated with hepatitis B virus (HBV) and hepatitis C virus infections, along with conditions such as nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Other important contributors include aflatoxin B1 exposure and chronic alcohol consumption.<sup>3,4</sup> Chronic hepatitis and liver cirrhosis lead to ongoing liver cell damage and regeneration, which increases



the risk of gene mutations. Furthermore, changes in the liver's microenvironment—such as chronic inflammation, liver cell regeneration, extracellular matrix alteration, and immune microenvironment imbalances—play a significant role in liver cancer onset and progression. In China, liver cancer is particularly prevalent, with both the incidence and mortality rates ranking among the highest for various cancer types. Notably, these rates are more pronounced in males than in females, predominantly associated with chronic HBV infection. Further, nonviral contributors, including alcohol intake and nonalcoholic fatty liver disease, are becoming increasingly significant. The majority of patients are identified at an advanced disease stage, which complicates treatment options and leads to a bleak prognosis.

Currently, liver cancer has various treatment options in China, including surgical resection, liver transplantation, local regional therapies (eg, interventional therapy, ablation therapy, radiotherapy), systemic therapies (eg, targeted therapy, immunotherapy, chemotherapy), and traditional Chinese medicine (TCM) treatment.<sup>5,6</sup> Surgery is the main curative method for patients with early-stage liver cancer, but most patients are diagnosed at an advanced stage and frequently require a comprehensive treatment approach. In recent years, emerging therapies, such as targeted therapy and immunotherapy, have brought new hope to patients with advanced liver cancer. However, challenges remain in liver cancer management, with overall treatment effectiveness requiring further improvement, and disparities in regional and medical resources making it challenging for some patients to receive timely and standardized treatment.

Traditional Chinese Medicine (TCM) is increasingly recognized for its potential in liver cancer treatment. Recent studies have supported its role, particularly as an adjunct therapy to alleviate symptoms, improve quality of life, and modulate immune responses.<sup>7–9</sup> This multifaceted approach provides a wider array of therapeutic options for patients. A central premise underlying TCM's efficacy in complex diseases like HCC is its multi-target, synergistic nature. Unlike single-target agents, TCM formulations and their bioactive components are postulated to exert therapeutic effects by simultaneously modulating multiple cellular pathways and the tumor microenvironment. Specifically, TCM treatments for liver cancer primarily include herbal decoctions, patent medicines, acupuncture, and massage. Among these, herbal formulas are individualized to meet patients' needs based on their specific conditions and constitutions. TCM treatment features a holistic view and syndrome differentiation, which comprehensively regulate patients' bodily functions, alleviate symptoms, and delay disease progression, especially exhibiting significant advantages in relieving suffering in patients with advanced disease and prolonging survival. For instance, curcumin inhibits HCC growth through MARCH1-mediated JAK2/STAT3 signaling regulation.<sup>10</sup> The SNKAF decoction can suppress HCC cell proliferation while simultaneously promoting apoptosis via PI3K/Akt/P53/FoxO signaling pathway modulation.<sup>11</sup> These findings derive from integrated metabolomics and network pharmacology analysis followed by *in vitro* validation in Huh7 and HepG2 cells. While the multi-omics approach is insightful, further *in vivo* validation is needed to confirm the network-predicted interactions within a physiological context. Evodiamine can exert anti-tumor effects in a synergistic manner through multiple aspects, including regulating immunity, inducing ferroptosis, and inhibiting the proliferation and migration of tumor cells (Figure 1). In recent years, the ongoing and extensive research into TCM modernization has generated a growing body of clinical evidence. This research indicates that TCM not only improves patients' resilience to alternative treatment modalities for hepatic carcinoma but also demonstrates the potential for integration with contemporary medical techniques. Huaier granules, Jinlong capsules, and Jianpi Huayu therapy, which collectively produce a synergistic effect, are examples of such integrative approaches.<sup>12–15</sup> This combination provides a more holistic level of support for patients undergoing hepatic carcinoma treatment. Furthermore, TCM research is highly relevant to contemporary drug design and development, particularly in the context of multi-target therapeutic strategies. Unlike conventional single-target agents, TCM compounds and formulations often produce synergistic effects via multiple biological pathways, aligning with the holistic concept of “systematic regulation” in network pharmacology. This multi-target characteristic of the compound aligns with the growing focus on polypharmacology and may guide the development of combination therapies and multi-target agents for hepatocellular carcinoma. By integrating modern approaches such as bioinformatics, molecular docking, and omics technologies, TCM research can elucidate complex networks of mechanisms of action and identify novel therapeutic targets, thus contributing to the development of more effective, personalized treatment regimens for HCC. This review aimed to investigate the underlying biological mechanisms (Figure 2) and clinical evidence associated with TCM extracts and formulations in HCC management. While several reviews have summarized the role of TCM in HCC, most have focused on either isolated mechanisms or clinical

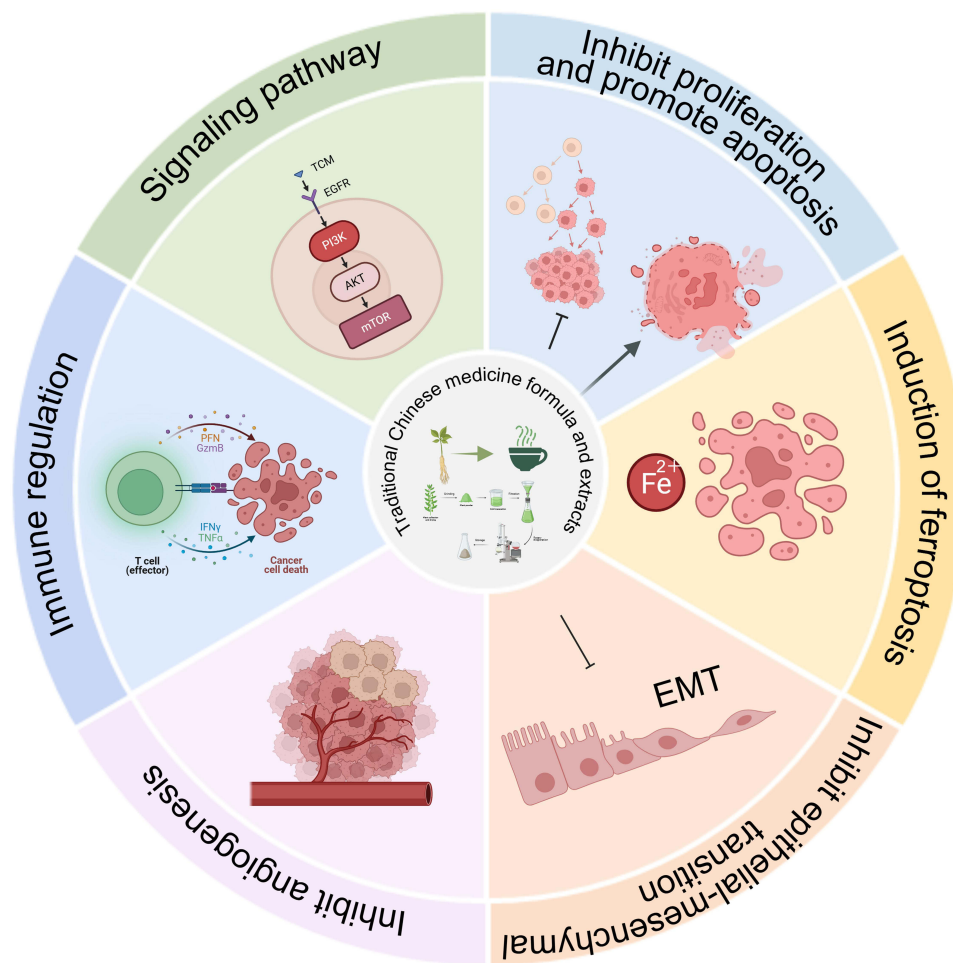


**Figure 1** The anti-tumor mechanism of evodiamine mainly manifests in the following four aspects: **(A)** Inhibiting tumor cell proliferation: achieved by regulating  $\beta$ -catenin. **(B)** Inducing tumor cell apoptosis: achieved by inhibiting NOD1 and triggering mitochondrial dysfunction. **(C)** Inducing ferroptosis in tumor cells: exerting effects by influencing reactive oxygen species levels and the activity of GPX4. **(D)** Regulating the tumor immune microenvironment: achieved by regulating the PI3K/AKT signaling pathway, enhancing the activity of CD4<sup>+</sup> T cells and CD8<sup>+</sup> T cells.

outcomes without integrating recent advances in network pharmacology and multi-omics research. This review provides a systematic synthesis of the latest evidence from both mechanistic studies and clinical trials, emphasizing TCM's multi-target and network-based attributes, thereby offering a comprehensive and translational perspective to researchers and clinicians. This analysis is anticipated to offer both theoretical foundations and practical insights for forthcoming research endeavors and clinical practices. By analyzing the literature, we summarize the effective components, mechanisms of action, and current clinical applications of TCM in HCC treatment, thereby providing safer and more effective treatment options for patients with liver cancer.

## Materials and Methods

We systematically searched the following databases: PubMed and Web of Science. The search keyword combinations included: (“traditional Chinese medicine” OR “Chinese herbal medicine” OR “herbal extract”) AND (“hepatocellular carcinoma” OR “liver cancer” OR “HCC”). We selected the literature related to hepatocellular carcinoma and traditional Chinese medicine published in the past decade. The literature screening criteria were as follows: the studies mainly investigated the effects of traditional Chinese medicine (TCM) monomers, compound formulas, or their extracts on hepatocellular carcinoma (HCC) and provided mechanism research or clinical data. We prioritized the inclusion of high-quality original research, systematic reviews, and key clinical trial reports, and excluded case reports and studies with incomplete data. To ensure the traceability and completeness of the research, the important reference works obtained from the search were traced and supplemented. Among the final references included, several were classic works published before 2015.



**Figure 2** Traditional Chinese medicine inhibits tumor progression through multiple pathways and optimizes the tumor microenvironment.

## Main Herbal Extracts and Formulas for HCC Treatment

The anti-HCC effects of TCM are achieved through a variety of biological mechanisms, reflecting its multi target approach. The following sections detail how specific herbs and formulas target key hallmarks of cancer progression, including uncontrolled cell proliferation, evasion of cell death, metastatic potential, angiogenesis and immune evasion. Understanding these interconnected mechanisms offers valuable insight into TCM's potential as a holistic therapeutic approach.

### Herbal Medicines and Their Extracts for HCC Treatment

Single herbal medicines refer to medicinal materials that are derived from a single plant, animal, or mineral source. For instance, the herb *Marsdenia tenacissima* mainly comes from the dried stems of the plant *M. tenacissima* in the family *Asclepiadaceae*, which induces apoptosis, inhibits tumor-associated angiogenesis, and improves immune function by targeting P53, JAK-1, and HIF1 $\alpha$ , thereby exerting therapeutic effects against liver cancer.<sup>16</sup> An additional illustration is the herb combination of *Shashen* and *Maidong*, which improved the percentage of CD8<sup>+</sup> T lymphocytes within the immune microenvironment of HCC and modulated their subgroup distribution.<sup>17</sup> This mechanism contributes to the immune regulatory effects aimed at liver cancer treatment. *Calculus bovis*, a dried gallstone from *Bos taurus domesticus* Gmelin, inhibits M2 macrophage polarization through the Wnt/ $\beta$ -catenin pathway, helping to inhibit liver cancer cell growth.<sup>18</sup> The *Astragalus*–*Atractylodes* herb pair regulates the interleukin-6 (IL-6)/STAT3 signaling pathway in H22 tumor tissues, thereby increasing CD8<sup>+</sup> T-cell proportion.<sup>19</sup> The *Dahuang*–*Dangshen* drug pair inhibits cell proliferation and metastasis and promotes cell apoptosis activity through the EGFR/AKT signaling pathway.<sup>20</sup> *Celastrol* can not only impede HCC cell migration but also provoke ferroptosis within these cancerous

cells.<sup>21,22</sup> Moreover, the combination of Astragali radix and Curcumae rhizoma has demonstrated effectiveness in suppressing HCC via the EGFR/AKT/mTOR signaling pathway, while simultaneously promoting lipid peroxidation-associated ferroptosis.<sup>23</sup>

In the field of liver cancer treatment, drugs that enhance immune function (eg, Astragalus, Ginseng, Ganoderma lucidum, Cordyceps),<sup>24–26</sup> demonstrate qi-invigorating and yin-nourishing effects (eg, Testudinis Carapax, Codonopsis, Ophiopogon, Lycium barbarum), soothe the liver and regulate qi (eg, Chaihu, Xiangfu, Yujin), and clear the liver and benefit the gallbladder (eg, Gentiana, Artemisia) are available. These drugs synergistically exert their effects through various mechanisms, capable of inhibiting tumor cell proliferation, inducing tumor cell apoptosis, improving immune function, alleviating inflammatory responses, and protecting liver cells, thereby demonstrating crucial value in liver cancer treatment.

Considering that TCM extracts exhibit a range of biological activities, including antioxidant and anti-inflammatory properties, they are considered promising candidates for developing new therapeutic approaches for liver cancer.<sup>27</sup> Several in vitro and in vivo studies have confirmed that TCM extracts exhibit significant antitumor characteristics against liver cancer. Common extracts include triterpenoid saponins, flavonoids, triterpenoid glycosides, steroid saponins, and alkaloids. These natural products improve and combat liver cancer through different pathways.

“Cinobufacini” is a TCM preparation extracted from the dried skin and glandular secretions of the Chinese giant toad, with main components, including bufadienolide and indole alkaloids. Current studies indicate that “Cinobufacini” inhibits HCC cell migration and invasion, suppresses HCC cell growth, and promotes apoptosis through the c-Met, PI3K/AKT, and MEK/ERK signaling pathways.<sup>28,29</sup> Curcumin inhibits cell proliferation by downregulating lincROR and inactivating Wnt/ $\beta$ -catenin signaling.<sup>30</sup> This mechanism is primarily supported by in vitro studies, with corroborating evidence from xenograft mouse models showing reduced tumor growth.<sup>30,31</sup> However, direct clinical evidence linking this specific molecular mechanism to patient outcomes remains to be established. Dai et al revealed that matrine promotes miR-199a-5p expression, inhibiting the HIF-1 $\alpha$  signaling pathway and epithelial-mesenchymal transition (EMT), thereby resisting HCC metastasis.<sup>32</sup> Studies have shown that sophocarpine can inhibit TGF- $\beta$ -induced EMT and exert antitumor effects by downregulating cancer stem cell-related pathways.<sup>33</sup> Moreover, ginsenoside compound K reduces Bclaf1 expression levels, thereby interfering with the glycolytic pathway regulated by HIF-1 $\alpha$ , ultimately inhibiting HCC cell proliferation.<sup>34</sup>

Ophiopogonin-B (OP-B) is a steroid saponin that is extracted from the tubers of Ophiopogon japonicus, which is a bioactive component of the Ophiopogon root and can exert anticancer effects against various malignant tumors. It suppresses cell proliferation, migration, invasion, and angiogenesis, thereby promoting apoptosis in HCC cells through multiple mechanisms.<sup>35</sup> The ethyl acetate extract derived from the detoxification formula Xiaozheng Yin can induce cell cycle arrest at the G0/G1 phase both in vitro and in vivo.<sup>36</sup> Further, it demonstrates inhibitory effects on HCC cell proliferation by downregulating the expression of the polycomb group gene product Bmi1 and interfering with the Wnt/ $\beta$ -catenin signaling pathway.<sup>37</sup>

Tanshinol, a polyphenolic compound that dissolves in water, is derived from *Salvia miltiorrhiza* Bunge and demonstrates a series of biological activities, including anti-inflammatory, anti-ischemic, and antiosteoporotic properties. Its anticancer effects, particularly in liver cancer, are mediated through PI3K-Akt signaling pathway modulation. In vitro, it inhibits HCC cell growth and colony formation, while inducing apoptosis in HepG2 cells and inhibiting their migration and invasion. In vivo, tanshinol inhibits the tumor growth and metastasis of HepG2 cells.<sup>38</sup> To quickly collect more information, we summarize the TCM and their extracts used for treating liver cancer in Table 1. We have discussed the herbal medicines and their extracts used to treat liver cell cancer. Next section focuses on the traditional Chinese medicine, compound formulas.

## Compound Formulations for Treating HCC

The potential value of herbal formulations in treating various diseases is well known. With a history of over 2000 years, they have demonstrated remarkable efficacy in many cases, making them important in global public healthcare systems, especially in East Asian countries.<sup>79</sup> The conceptual framework underlying TCM in liver cancer management primarily derives from the pathogenesis characterized by “deficiency at the source combined with excess in superficial aspects”. This approach highlights a holistic perspective and adheres to the principle of syndrome differentiation in treatment.

**Table 1** TCM and Its Extracts for HCC Treatment

TCM and Its Extracts	Effect	Function Pathway	References
Marsdenia tenacissima	Promotes apoptosis	Targets P53, JAK-1 and HIF1 $\alpha$	[16]
Shashen-Maidong herb pair	Improves immune function	Improves the proportion of CD8+T cells	[17]
Astragalus-Atractylodes Herb Pair	Improves immune function	The IL-6/STAT3 pathway	[19]
Dahuang-Dangshen drug pairs	Inhibits proliferation and migration and promotes apoptosis	The EGFR/AKT pathway	[20]
Celastrol	Inhibits migration	Inhibits the ROCK2-mediated phosphorylation	[21]
Astragali radix-Curcumae rhizoma herb pair	Induces ferroptosis	Via HIF-1 $\alpha$ /HO-1/GPX4 axis	[23]
Astragalus Membranaceus and Curcuma Wenyujin	Promotes Vascular Normalization	Increases expression of CD34 and reduces expression of HIF1 $\alpha$	[39]
Calculus bovis	Inhibits M2 macrophage polarization	The Wnt/ $\beta$ -catenin pathway	[18]
Cinobufacini	Prevents migration and invasion	The c-Met and PI3K/AKT and MEK/ERK pathways	[28,29]
Curcumin	Suppresses proliferation	Inactivation of Wnt/ $\beta$ -catenin signaling	[30]
Matrine	Exhibits significant anti-metastatic	Enhances miR-199a-5p expression and impairs HIF-1 $\alpha$ signaling	[32]
Sophocarpine	Inhibits EMT	Via TGF- $\beta$	[33]
Ginsenoside Compound K	Inhibits proliferation	Downregulates the expression of Bclaf1	[34]
Ophiopogonin-B	Inhibits the metastasis and angiogenesis	Inhibits EphA2/Akt	[35,40]
Ethyl acetate extraction from Jiedu Xiaozheng Yin	Inhibits proliferation	The Wnt/ $\beta$ -catenin signaling	[36,37]
Tanshinol	Inhibits the growth, migration and invasion	The PI3K-AKT pathway	[38]
Echinacoside	Inhibits the proliferation, invasion and migration	Via the miR-503-3p/TGF- $\beta$ 1/Smad axis	[41]
Polygonum cuspidatum Extract	Inhibits suspension growth	Relates to ROS generation and FAK downregulation	[42]
Ligustrum lucidum Ait. fruit extract	Induces apoptosis and cell senescence	Upregulation of p21	[43]
Extract of Marsdenia tenacissima (Roxb.) Moon [Apocynaceae]	Inhibits Angiogenesis	Represses the expression of VEGF, VWF, PDGF, and PDGFRB	[44]
Arenobufagin	Induces apoptosis and autophagy	Inhibition of PI3K/Akt/mTOR pathway	[45]
Apigenin	Induces apoptosis and autophagy	Inhibition of PI3K/Akt/mTOR pathway	[46]
Ganoderma lucidum	Induces apoptosis and cell cycle arrest	Regulates the PI3K/AKT pathway	[47]

(Continued)

**Table 1** (Continued).

<b>TCM and Its Extracts</b>	<b>Effect</b>	<b>Function Pathway</b>	<b>References</b>
Astragaloside IV and Curcumin	Inhibits tumor growth and angiogenesis	Upregulates expression of miR-122 and downregulates expression of miR-221	[48]
Combination of Astragali Polysaccharide and Curcumin	Induces Tumor Vascular Normalization	Downregulates expression of CD31 and upregulates expression of NG2	[49]
Cantharidin	Activates antitumour immunity	Regulates EZH2/H3K27me3-dependent cell cycle progression	[50]
Bufalin	Inhibits angiogenesis, migration, invasion and adhesion	The $\beta$ -catenin/TCF pathway	[51–53]
Epigallocatechin gallate (EGCG)	Inhibits tumor growth and angiogenesis	The MAPK/ERK1/2 and PI3K/AKT/HIF-1 $\alpha$ /VEGF pathways	[54]
Galangin	Induces G0/G1 phase arrest and cell apoptosis	The PI3K-Akt pathway	[55]
Anhydroicaritin	Suppresses proliferation, invasion and metastasis	The PI3K/AKT pathway	[56]
Platycodin D, triterpenoid saponin	Inhibits adhesion, migration and invasion and induces apoptosis	Up-regulates PARP and Bax	[57]
Dioscin	Induces apoptosis	Regulates of TP53, BAX, BCL2 and cleaves CASP3	[58]
Segetoside I	Induces apoptosis	Up-regulation of Bax and down-regulation of Bcl-2	[59]
Tubeimoside I	Inhibits the proliferation	Mediates a cascade of apoptosis pathways	[60]
Extracts of Qizhu decoction	Inhibits the proliferation and migration	Suppresses NF- $\kappa$ B signaling	[61]
Scutellaria barbata D. Don and Oldenlandia diffusa (Willd.) Roxb crude extracts	Inhibits growth, migration, invasion	Regulates circRNA expression	[62]
Luteolin	Induces apoptosis	Inhibits the AKT/osteopontin pathway	[63–65]
Emodin	Inhibits growth and induces apoptosis	Blocks activation of STAT3	[66]
Diosgenin	Suppresses proliferation	Inhibits STAT3 pathway	[67]
Evodiamine	Inhibits proliferation, migration	Down-regulates the expression of STAT3-mediated genes	[68]
Cantharidin	Inhibits the proliferation and promotes apoptosis	Regulates the JAK2/STAT3 and PI3K/Akt pathways	[69]
Artemisia capillaris extract AC68	Induces apoptosis	Blocks the PI3K/AKT pathway	[70]
An ethyl acetate fraction of Artemisia capillaris (ACE-63)	Induces apoptosis and anti-angiogenesis	Inhibits PI3K/AKT pathway	[71]
Saponin D (designated SB365)	Inhibits growth and angiogenesis	Modulates of the PI3K/Akt/mTOR pathway	[72]
Artemisia Capillaris leaves	Inhibits proliferation and induces apoptosis	Blocks the PI3K/AKT pathway	[73]

(Continued)

**Table 1** (Continued).

TCM and Its Extracts	Effect	Function Pathway	References
Rheum palmatum extract	Reduces viability, migration, and invasion	Inhibits STAT3	[74]
Evodiamine exerts	Suppresses growth and angiogenesis	Inhibits $\beta$ -catenin	[75]
Artemisia capillaris extract	Suppresses the growth and migration	Modulates of the IL-6/STAT3 pathway	[76]
Morusin	Induces apoptosis and inhibits anti-angiogenesis	Increases the expression of active caspase-3 and the Bax/Bcl-2	[77]
Plumbagin	Inhibits angiogenesis	PI3K-Akt, VEGF/KDR and Angiopoietins/Tie2	[78]

TCM posits that liver cancer development is intricately associated with a depletion of righteous qi alongside an internal buildup of pathogenic toxins. Such a righteous qi deficiency facilitates the invasion of these harmful toxins, subsequently causing a qi and blood imbalance, internal toxin accumulation, and ultimately, tumor formation. Concurrently, TCM emphasizes a holistic view, considering the human body as an organic whole, where the pathological changes in liver cancer involve not only the liver but also the spleen, stomach, kidneys, and other organs. Therapeutic approaches must comprehensively assess the patient's overall condition by identifying different syndromes through syndrome differentiation. This process may reveal various issues, including liver qi stagnation, spleen deficiency syndrome, and damp-heat toxin accumulation syndrome, among others. Strategies, such as tonifying the righteous qi while expelling pathogenic factors, soothing the liver and fortifying the spleen, and clearing heat and promoting diuresis, need to be implemented. These methods aim to restore bodily equilibrium, impede tumor progression, alleviate symptoms, and improve the overall quality of life of patients.

To date, over 5000 herbal medicines have been recorded and practiced in Asia, and the same herbs frequently exhibit different functions in various formulations due to their interactions in various combinations. An effective and successful formula typically undergoes multiple modifications in dosage or herb selection.<sup>79</sup> For instance, the Xiaoi Jiedu recipe exerts its antitumor effects through the miR-200b-3p/Notch1 axis.<sup>80</sup> The Pulsatilla decoction exerts its cytotoxic effects on HCC cells by triggering apoptotic pathways and suppressing cancer cell proliferation.<sup>81</sup> Further, the Sanleng Jiashen formula demonstrates significant efficacy in counteracting the aggressive proliferation of liver cancer tissues and concurrently impedes angiogenesis.<sup>82</sup> To provide a clearer and more intuitive understanding of the molecular mechanisms by which herbal formulas exert antitumor effects in liver cancer, Table 2 summarizes the TCM formulas used for liver cancer treatment. After reviewing individual herbs, their extracts, and formulations, we will now examine their mechanisms of action.

**Table 2** TCM Formula for HCC Treatment

TCM	Composition	Effect	Function Pathway	References
Huqi formula	Viscum coloratum, Astragalus membranaceus, Salvia miltiorrhiza, etc	Induces apoptosis	Downregulates p-PI3K, p-AKT, and p-mTOR expression	[83]
Fuzheng Jiedu Xiaoji formulation	Codonopsis pilosula, Astragalus membranaceus, Atractylodes macrocephala, etc	Inhibits proliferation and migration	The AKT/CyclinD1/p21/p27 pathways	[84]

(Continued)

Table 2 (Continued).

TCM	Composition	Effect	Function Pathway	References
Jianpi Huayu decoction	Atractylodes macrocephala Koidz, Curcuma zedoaria Roscoe, Poria cocos, etc	Inhibits EMT	Downregulates the transfer of miR-23a-3p	[85]
Jiedu Xiaozheng Yin decoction	Hedyotis diffusa Willd, Sophora flavescens, Psuedobulbus cremastrae and Spica prunellae	Induces apoptosis and inhibits tumor angiogenesis	Downregulates the expression of VEGF-A and VEGFR-2	[86,87]
Fuzheng Qingjie recipe	Astragalus membranaceus, Ligustrum lucidum, Ganoderma lucidum, etc	Induces apoptosis	Via P38 MAPK activation	[88,89]
Herb Mixture Qingjie Fuzheng Granules	Hedyotis diffusa Willd, malt, Astragalus, and Scutellaria barbata D. Don	Induces apoptosis	Increases the expression of Fas, FasL, Bax	[90]
Huanglian decoction	Coptidis Rhizoma, Zingiberis Rhizoma, Folium Artemisiae Argyi, and Mume Fructus	Suppresses the growth	Reduces CCNBI expression	[91]
Xiaoai Jiedu recipe	Spreading Hedyotis Herb, Appendiculate Cremastra Pseudobulb, etc	Stimulates autophagy	Via the AKT/mTOR pathway	[92]
Huayu Wan (HYW)	Crassostrea gigas, Hirudo nipponi, Tabanus, etc	Inhibits the malignant proliferation	The PI3K/AKT/VEGFA pathway	[93]
Ruangan Lidan decoction	Chaihu, Scutellaria baicalensis, Corydalis, etc	Inhibits the growth and metastasis	Downregulates miR-9-5p and upregulates PDK4	[94]
Yangyin Fuzheng Jiedu prescription	Hedysarum multijugum Maxim, Atractylodes macrocephala Koidz, Radix Bupleuri, etc	Immunoregulatory effects	Alleviates T cell exhaustion	[95]
Yupingfeng San	Huangqi, Baizhu and Turcz	Anti-proliferation and pro-apoptosis	The MAPK and JAK2-STAT3 pathway	[96,97]
Gupi Xiaoji Prescription	White Ginseng, Astragalus membranaceus, Scutellaria barbata, etc	Inhibits the proliferation and migration	Up-regulates MFN1 and MFN2, down-regulates the expression of FIS1	[98]
Shi-pi-xiao-ji (SPXJ) herbal decoction formula	Hedysarum multijugum Maxi, Panax Ginseng C. A. Mey, Fructus Ligustri Lucidi, etc	Inhibits proliferation, invasion, and migration	Upregulates the expression of ACAT1 protein	[99,100]
Jianpi Huatan Recipe (JPHTR)	Brassica juncea (L.) Czern, Perilla frutescens (L) Britt and Raphanus sativus L	Delays the development of HCC	Regulates the expression of Il-6/ Jak2/Foxo3	[101]
Huqizhengxiao (HQZX) Decoction	Hu ji sheng, Huang qi, E zhu, Yu jin, San qi, etc	Inhibits the growth and induces tumor apoptosis.	The STAT3 and ERK signal pathway.	[102]
Hu-Qi-Zheng-Xiao Decoction	Mistletoe, astragalus, scutellaria baicalensis, white-flowered snakeroot, etc	Inhibits EMT, LCSC and Angiogenic Process	Suppresses the HIF-1 $\alpha$ Pathway	[103]
Sinikangai fang (SNKAF) decoction	Hedyotis diffusa Willd, Eupolyphaga sinensis Walker, etc	Suppresses proliferation and induces apoptosis	Via PI3K/Akt/P53/FoxO signaling axis	[11]
Pulsatilla decoction	Radix Pulsatillae, Cortex Phellodendri, Rhizoma Coptidis, and Cortex Fraxini	Inhibits proliferation	Via the PI3K-AKT, IL-17, and TNF pathways	[81]

## Biological Mechanisms of Herbal Extracts and Formulas for HCC Treatment

The anti-HCC effects of TCM are achieved via various biological mechanisms, reflecting its multi-targeted approach. The following sections detail how specific herbs and formulas target key hallmarks of cancer progression, including uncontrolled cell growth, evasion of cell death, metastatic potential, angiogenesis, and immune evasion. Understanding these interconnected mechanisms offers insights into TCM's potential as a comprehensive therapeutic strategy. Current research reveals several specific mechanisms, though their evidence strength and translational maturity vary significantly across different compounds and formulations. In Table 3, we summarize the mechanisms of action corresponding to different traditional Chinese medicines and the stage of evidence supporting these mechanisms.

### Inhibit HCC Cell Growth, Proliferation, and Migration, and Promote Apoptosis

TCM demonstrates significant potential in inhibiting HCC cell growth, proliferation, and migration, and promoting apoptosis. Recent studies have shown that both many herbal extracts and classical formulas primarily exert anti-HCC effects by inducing apoptosis. However, the strength and validation level of these mechanistic findings vary considerably. One study revealed that under the induction of des- $\gamma$ -carboxy prothrombin, Cinobufacini inhibits HCC cell growth by acting on c-Met and the PI3K/AKT and MEK/ERK signaling pathways, thereby promoting HCC cell apoptosis while reducing their invasion and migration capabilities. We confirmed the therapeutic potential of Cinobufacini for HCC through in vitro experiments; in vivo experiments further demonstrated the potential of combining cinobufacini with c-Met inhibitors for the treatment of primary HCC. In a mouse model of hepatocellular carcinoma, Cinobufacini demonstrated a significant anti-tumor effect also.<sup>29</sup> Both Xihuang Pills and The Huqi formula (HQF) exert their inhibitory effects on hepatocellular carcinoma through the PI3K/AKT/mTOR pathway. Both directly or indirectly inhibit multiple key nodes in this pathway, such as p-PI3K, p-AKT, and p-mTOR, cutting off the growth and survival signals of cancer cells and thereby inducing the apoptosis of liver cancer cells. The PI3K/AKT/mTOR pathway has now become an extremely attractive target

**Table 3** Representative TCM Compounds/Formulas, Their Proposed Anti-HCC Mechanisms, and Stage of Evidence

TCM Agent	Proposed Anti-HCC Mechanisms	Key Targets/Pathways	Current Stage of Evidence
Curcumin	Induces apoptosis and inhibits proliferation, angiogenesis and modulates immunity	JAK2/STAT3, Wnt/ $\beta$ -catenin, TLR4/NF- $\kappa$ B	Preclinical (in vitro + in vivo) <sup>10,30,31</sup>
Cinobufacini	Inhibits proliferation, migration and EMT and induces apoptosis	c-Met, PI3K/AKT, MEK/ERK	Preclinical (in vitro + in vivo) <sup>28,29</sup>
Evodiamine	Induces apoptosis and ferroptosis, inhibits proliferation and modulates immune microenvironment	$\beta$ -catenin, NOD1, ROS/GPX4, PI3K/AKT	Preclinical (primarily in vitro) <sup>68,75</sup>
Astragali–Curcumae Herb Pair (ACHP)	Inhibits proliferation and induces ferroptosis	EGFR/AKT/mTOR, HIF-1 $\alpha$ /HO-1/GPX4	Preclinical (in vitro + in vivo) <sup>23</sup>
Polyphyllin I	Induces ferroptosis and inhibits metastasis	Nrf2/HO-1/GPX4, mitochondrial function	Preclinical (in vitro + in vivo, with inhibitor rescue) <sup>104</sup>
Jiedu Xiaozheng Yin Decoction	Induces apoptosis and inhibits angiogenesis and proliferation	Mitochondrial pathway, VEGF-A/VEGFR-2, Bmi1/Wnt/ $\beta$ -catenin	Preclinical (in vitro + in vivo) <sup>36,37,86,87</sup>
Fuzheng Qingjie Granules	Induces apoptosis and enhances immunity	Mitochondrial apoptotic pathway, p38 MAPK, CD4+/CD8+ T cells	Preclinical (in vitro + in vivo) <sup>88,89</sup>
Jianpi Huayu Decoction	Inhibits EMT and metastasis	Exosomal miR-23a-3p/Smad signaling	Preclinical (in vitro + in vivo); <sup>85</sup> Clinical (RCT) <sup>15</sup>

for anti-cancer drugs. Most of the studies on the inhibitory effects of Xihuang Pills and Huqi Prescription on hepatocellular carcinoma are *in vitro* experiments and animal models, with relatively few clinical trials.<sup>83,105</sup> Further, both Platycodin D and Yin Yang Gong Ji pill predominantly trigger apoptotic processes, thereby effectively hampering HCC cell migration and invasion.<sup>57,106</sup> Jiedu Xiaozheng Yin decoction, Fuzheng Qingjie recipe, Xiaoi Jiedu recipe, Yanggan Jiedu Sanjie formula, *Ligustrum lucidum* Ait. fruit extract, Arenobufagin, Apigenin, *Ganoderma lucidum*, and Yupingfeng San also suppressed liver cancer cell proliferation by inducing apoptosis.<sup>43,45–47,86,88–90,92,96,107</sup>

Curcumin, a bioactive component derived from the *Curcuma longa* plant, is recognized as a natural polyphenol characterized by its biological properties, comprising anti-inflammatory, antioxidant, and antimicrobial effects. Curcumin suppresses cell proliferation by downregulating lincROR and inactivating Wnt/ $\beta$ -catenin signaling. lincROR can stabilize  $\beta$ -catenin and facilitate its translocation to the nucleus. After curcumin reduces the level of lincROR, the stability of  $\beta$ -catenin and its nuclear translocation decrease, leading to decreased transcription of its target oncogenes (such as c-Myc, Cyclin D1), thereby exerting tumor-suppressive effects.<sup>30</sup> Dai et al revealed that matrine exhibits significant inhibitory effects on HCC metastasis, attributed to miR-199a-5p upregulation, causing HIF-1 $\alpha$  signaling pathway blockade and EMT process inhibition. miR-199a-5p is a crucial microRNA that often acts as a tumor suppressor in HCC. Its upregulation inhibits cancer progression. miR-199a-5p directly targets the mRNA of HIF-1 $\alpha$ , thereby reducing HIF-1 $\alpha$  protein levels. HIF-1 $\alpha$  is a hypoxia-inducible factor that promotes hypoxic adaptive responses in the tumor microenvironment, such as angiogenesis and metabolic reprogramming, and is crucial for cancer metastasis. The downstream effects of HIF-1 $\alpha$  include activating EMT-related transcription factors, thereby driving cells to transform from an epithelial phenotype to a mesenchymal phenotype, enhancing their migration and invasion capabilities. Scutellamine blocks EMT through this axis and limits the metastatic potential of HCC cells.<sup>32</sup> Further, ginsenoside compound K reduces Bclaf1 expression in hypoxic liver cancer cells, blocking HIF-1 $\alpha$ -mediated glycolysis and inhibiting cell proliferation.<sup>34</sup>

Some herbal medicines act on the cell cycle to suppress liver cancer cell proliferation and migration. *In vitro* studies indicate that the Chinese herbal formulation QHF effectively inhibits HCCLM3 cell proliferation by inducing cell cycle arrest specifically at the G2/M phase, while simultaneously promoting apoptosis and suppressing cell migration and invasion. Further, QHF downregulated the p-c-Met protein expression in HCCLM3 cells. Considering the important role of c-Met in HCC metastasis, *in vivo* investigations further demonstrated that the c-Met gene improves tumor growth and facilitates lung metastasis in nude mice. Notably, QHF treatment appears to mitigate tumor lung metastasis by targeting and inhibiting the HGF/c-Met signaling pathway.<sup>108</sup> Furthermore, Yu et al indicate that the Dahuang–Dangshen drug combination may impede cell proliferation and migration while promoting apoptosis through EGFR/AKT signaling pathway modulation.<sup>20</sup> Furthermore, Ophiopogonin-B, Ethyl acetate extract from Jiedu Xiaozheng Yin, Tanshinol, Echinacoside, Huanglian decoction, Huayu Wan, Ruangan Lidan decoction, and Yupingfeng San inhibited cell growth, proliferation, and migration, thereby exerting antitumor effects.<sup>35,37,38,40,41,91,93,94,96</sup>

## Inducing Ferroptosis

Ferroptosis represents an emerging paradigm of oxidative cellular demise. During this process, increased unsaturated fatty acid levels present in the cell membrane, facilitated by divalent iron or lipoxygenase, were used to instigate lipid peroxidation. This phenomenon diminishes cellular antioxidant defenses, increases lipid peroxidation-derived reactive oxygen species (ROS) levels, and promotes the accumulation of intracellular ferrous ions. These alterations disrupt the existing redox balance, causing oxidative cell death.<sup>109</sup> Increasing evidence suggests that tumor cells exhibit increased susceptibility to ferroptosis due to reprogramming of iron metabolism, elevated oxidative stress levels, and a high dependence on the GPX4-mediated antioxidant defense system.<sup>110</sup> The active components of traditional Chinese medicine may preferentially induce ferroptosis in tumor cells by moderately inhibiting the activity of GPX4 or enhancing lipid peroxidation, while sparing normal cells that maintain intact redox homeostasis. Moreover, ferroptosis does not occur in isolation; excessive accumulation of lipid reactive oxygen species (ROS) can also damage mitochondrial integrity and activate apoptotic signaling pathways, indicating a potential synergistic interaction between ferroptosis and apoptosis in the anti-tumor effects mediated by traditional Chinese medicine.<sup>111</sup> Recent studies have indicated the crucial role of ferroptosis in tumor development, particularly in HCC. Inducing ferroptosis not only inhibits tumor cell

growth and reverses tumor formation but also improves the effectiveness of immunotherapy and boosts the body's immune response against tumors. Considering these insights, triggering ferroptosis has emerged as a promising strategy for cancer treatment.<sup>112</sup> Certain TCM have combat liver cancer by inducing ferroptosis. For instance, Polyphyllin I (PPL), a steroid saponin derived from the root of *Paris polyphylla*, exhibits extensive antitumor effects. PPL inhibits HCC cell proliferation, invasion, and metastasis in a dose-dependent manner by increasing the levels of ROS and malondialdehyde. Further, it promotes  $\text{Fe}^{2+}$  accumulation, decreases glutathione (GSH) levels, and inhibits xCT and GPX4 expression, thereby triggering HCC cell ferroptosis. The ferroptotic effect of PPL is associated with its interaction with proteins, such as Nrf2, HO-1, and GPX4, which are part of the regulatory mechanism of the Nrf2/HO-1/GPX4 antioxidant pathway. Further, PPL causes structural damage to mitochondria and reduces the mitochondrial membrane potential. The compound Ferrostatin-1 has alleviated the mitochondrial damage induced by PPL by inhibiting ferroptosis. Overall, these findings indicate that PPL not only exacerbates mitochondrial injury but also initiates ferroptosis through the Nrf2/HO-1/GPX4 pathway, thereby hindering HCC cell proliferation, invasion, and metastasis and providing a new approach for liver cancer treatment.<sup>104</sup>

Shipi Xiaoji formula is a TCM formulation that demonstrates antitumor properties against HCC cells through ferroptosis induction. This phenomenon involves an increase in the intracellular  $\text{Fe}^{2+}$  and ROS levels, alongside a decrease in the GSH levels. Further, there are changes in the mitochondrial structure and an upregulation of proteins that promote ferroptosis, including ACSL4 and LPCAT3. In contrast, protein levels that inhibit ferroptosis, such as xCT and GPX4, were significantly reduced.<sup>99</sup> Celastrol, a natural triterpenoid compound derived from the root bark of *Tripterygium wilfordii*, exhibits a range of biological activities and pharmacological effects. It has induced ferroptosis in HCC by modulating the expression of GSTM1, positioning it as a promising new therapeutic agent for HCC treatment with potential clinical applications.<sup>22</sup>

The induction of ferroptosis by TCM components like PPL, ACHP, and Celastrol represents a promising and emerging mechanism. Current evidence for these compounds is robust at the cellular level, demonstrating clear increases in ROS,  $\text{Fe}^{2+}$ , and lipid peroxidation markers alongside decreased GSH and GPX4.<sup>22,23,104</sup> Notably, several of these studies have employed specific ferroptosis inhibitors (eg, Ferrostatin-1) as controls to confirm the mode of cell death, adding rigor. In vivo validation has been reported for PPL and ACHP in mouse xenograft models, showing tumor suppression associated with ferroptosis markers.<sup>23,104</sup> A common thread among these diverse TCM agents is their downstream impact on the Nrf2/HO-1/GPX4 or HIF-1 $\alpha$ /HO-1/GPX4 antioxidant axis, suggesting a convergent pathway for TCM-induced ferroptotic vulnerability in HCC cells.

## Epithelial-Mesenchymal Transition Inhibition

EMT refers to the process by which epithelial cells lose their polarity, cell–cell junctions, and epithelial characteristics, acquiring mesenchymal cell traits, including elongated cell morphology, enhanced motility, and increased invasiveness. This process involves significant changes in the cell morphology, intercellular junctions, cytoskeleton, and gene expression.<sup>113,114</sup> EMT plays a crucial role in the initial stages of tumor metastasis during cancer progression, when cells lose intercellular junctions due to the loss of E-cadherin and gain stronger migratory abilities to invade adjacent or distant tissues.<sup>115</sup> In vitro experiments have shown that after treatment with cinobufacini, HepG2 cells upregulate the epithelial marker E-cadherin and downregulate the mesenchymal markers N-cadherin, Vimentin, and EMT transcription factors. Meanwhile, the phosphorylation level of the c-Met receptor is inhibited, and the activation of its downstream MEK1/2 and ERK1/2 is also attenuated. This indicates that cinobufacini exerts an inhibitory effect on the c-Met/ERK signaling pathway, leading to the attenuation of EMT and thereby inhibiting the migration and invasion of HepG2 cells.<sup>28</sup> Currently, the evidence regarding the mechanism by which Cinobufacini acts on the c-Met/ERK signaling pathway through the inhibition of epithelial-mesenchymal transition (EMT) is in the “early laboratory research stage”, mainly derived from in vitro cell experiments and some animal experiments. In in vitro cell experiments and animal models, Jianpi Huayu decoction inhibits epithelial–mesenchymal transition (EMT) of hepatocellular carcinoma (HCC) cells. The underlying mechanism may be partially associated with its ability to reduce exosome-mediated miR-23a-3p transfer and block the Smad signaling pathway. However, this mechanism has not been validated in clinical studies.<sup>85</sup>

Hu et al revealed that Yanggan Jiedu Sanjie (YGJDSJ) can inhibit TGF- $\beta$ 1-induced EMT in human liver cancer cells. YGJDSJ reverses the morphological changes induced by TGF- $\beta$ 1 in Bel-7402 cells and regulates the expression levels of the EMT markers E-cadherin and N-cadherin in Bel-7402 cells. Furthermore, YGJDSJ effectively suppresses the adhesion, migration, and invasion abilities of TGF- $\beta$ 1-induced Bel-7402 cells.<sup>116</sup> Moreover, matrine, sophocarpine, cantharidin, and scorpion in TCM inhibit EMT, thereby exerting antitumor effects.<sup>32,33,50,117</sup>

## Angiogenesis Inhibition

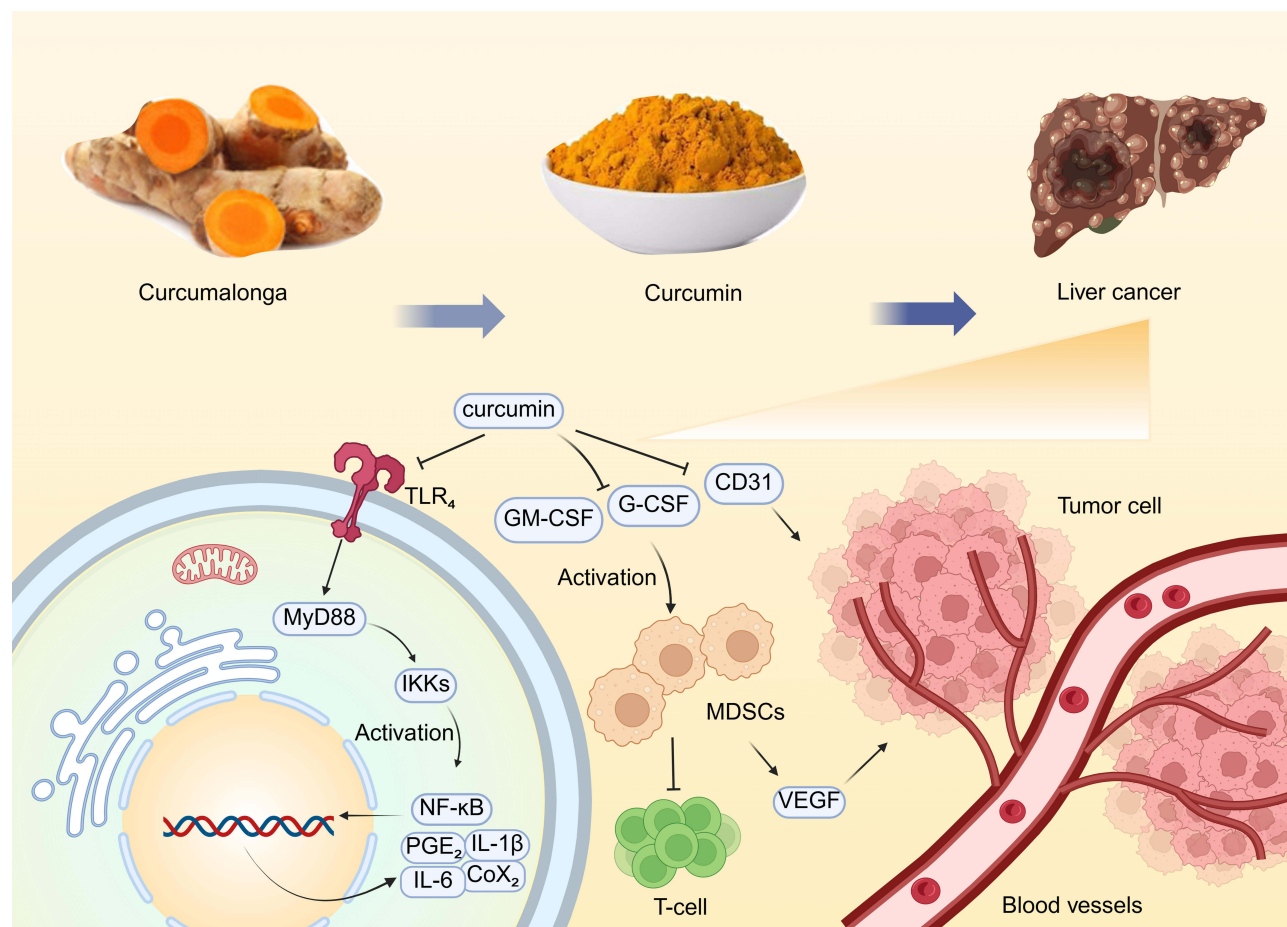
Angiogenesis plays a multifaceted, important role in liver cancer progression. It supports tumor growth by providing oxygen and nutrients to tumor cells.<sup>118,119</sup> Concurrently, new blood vessels provide a pathway for tumor cells to enter the bloodstream, thereby promoting tumor invasion and metastasis.<sup>120</sup> Further, various cells involved in the angiogenesis process (eg, hepatic stellate cells, tumor-associated macrophages) alter the tumor microenvironment, thereby promoting angiogenesis and forming a vicious cycle.<sup>121</sup> Rich angiogenesis also affects the sensitivity of liver cancer to treatment, whereas antiangiogenic therapy provides new approaches for liver cancer treatment. Jiedu Xiaozheng Yin, a TCM formula commonly composed of honeysuckle, forsythia, astragalus, codonopsis, and white atractylodes, can significantly reduce the tube formation ability and angiogenesis levels of human umbilical vein endothelial cells (HUVECs) in tumors *in vivo*, while decreasing the microvascular density of tumors. Comprehensive investigations revealed that Jiedu Xiaozheng Yin significantly suppressed the expression levels of vascular endothelial growth factor A (VEGF-A) and its receptor, vascular endothelial growth factor receptor 2 (VEGFR-2), in both HepG2 cells and HUVECs. Furthermore, it demonstrated considerable inhibitory effects on indicators associated with tumors. Jiedu Xiaozheng Yin can also interfere with the key signaling pathways mediated by VEGF-A/VEGFR-2, such as the PI3K/Akt/mTOR and Ras/Raf/MEK/ERK pathways, to inhibit the proliferation, migration, and survival signals of endothelial cells, thereby weakening the pro-angiogenic dynamics of the tumor microenvironment. In addition, several active components of this compound may act synergistically by targeting multiple processes, including endothelial cell apoptosis, matrix remodeling, and the synthesis of pro-angiogenic factors, forming a comprehensive network inhibiting vascular generation, ultimately reducing the density of tumor microvessels and inhibiting tumor growth. The evidence regarding the inhibitory effect of the Jiedu Xiaozheng Yin on the tumor angiogenesis and its molecular mechanism primarily derives from *in vitro* experiments and *in vivo* animal model studies. Randomized controlled clinical trials and high-quality clinical studies are currently lacking to directly verify this anti-angiogenic mechanism. The clinical relevance and translational value of this mechanism require further clinical research for confirmation.<sup>87</sup>

Curcumin, the active component of turmeric, has various biological activities, including promoting apoptosis and anti-inflammatory effects. Recent studies have revealed that it suppresses the growth of various cancers. Research reveals that curcumin (Figure 3) inhibits liver cancer growth by reducing the number of myeloid-derived suppressor cells and subsequently disrupting the angiogenesis process.<sup>31</sup> TCM, such as Ophiopogonin-B, *M. tenacissima*, Astragaloside IV, and curcumin, inhibits tumor-associated angiogenesis, thereby exerting antitumor effects.<sup>16,35,40,44,48</sup>

## Immune Regulation

Immune regulation plays a crucial role in liver cancer occurrence, development, and treatment, providing new ideas for liver cancer treatment. Fuzheng Qingjie (FZQJ) granules represent a composite TCM that has been used as a supplementary therapy in treating gastrointestinal malignancies. FZQJ has enhanced the proportion of CD4<sup>+</sup> T lymphocytes and natural killer cells, while improving the CD4<sup>+</sup>/CD8<sup>+</sup> T cell ratio and increasing serum tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) levels. This indicates that FZQJ may exert antiliver cancer effects by modulating the immune function.<sup>89</sup> Research has revealed that the Yangyin Fuzheng Jiedu prescription (FZP) significantly enhances the immune organ index and increases the counts of CD8<sup>+</sup> and CD3<sup>+</sup> T lymphocytes in both the spleen and peripheral blood of H22 tumor-bearing mice. Further, FZP treatment reduced the expression levels of PD-1, TIGIT, and TIM3 within CD8<sup>+</sup> T cells, alongside a decrease in pro-inflammatory cytokine secretion such as IL-10, IL-4, IL-6, and IL-1 $\beta$ . FZP improves the immunosuppressive microenvironment by alleviating T-cell exhaustion through various pathways.<sup>95</sup>

Research has revealed that the Shashen–Maidong herbal combination can improve the ratio of CD8<sup>+</sup> T lymphocytes in the immune microenvironment associated with liver cancer, as evidenced by both laboratory studies and live models.



**Figure 3** Curcumin can exert its effects through multiple mechanisms: Firstly, it inhibits the TLR4/NF- $\kappa$ B signaling pathway and downregulates the expression of inflammatory factors, including IL-6, IL-1 $\beta$ , PGE<sub>2</sub> and COX-2; Secondly, it reduces the secretion of granulocyte-macrophage colony-stimulating factor (GM-CSF) and granulocyte colony-stimulating factor (G-CSF) in tumor tissues, thereby inhibiting the generation of myeloid suppressive cells (MDSCs); Thirdly, it inhibits angiogenesis by downregulating the expression of CD31.

This herbal pair not only changes the distribution of CD8<sup>+</sup> T-cell subpopulations but also stimulates these cells to produce various immune mediators, including IL-2, TNF- $\alpha$ , IFN- $\gamma$ , granzyme B, and perforin.<sup>17</sup> Further, Bao et al revealed that the Shuihonghuazi Formula improves the absorption and utilization of linoleic acid and oleic acid in rats with liver cancer, thereby increasing arachidonic acid-like substances and boosting the overall immune response of the organism.<sup>122</sup> Further, TCM, such as *M. tenacissima* and the Astragalus–Atractylodes herb pair, can also exert antitumor effects by regulating the body's immune function.<sup>16,19</sup>

At present, most mechanisms by which traditional Chinese medicine regulates immune function and exerts anti-tumor effects are derived from in vitro and animal model studies. This evidence comes from preclinical and observational studies but lacks rigorously designed clinical randomized controlled trials to verify its effects on immune function and clinical outcomes in liver cancer patients.

## Signaling Pathways

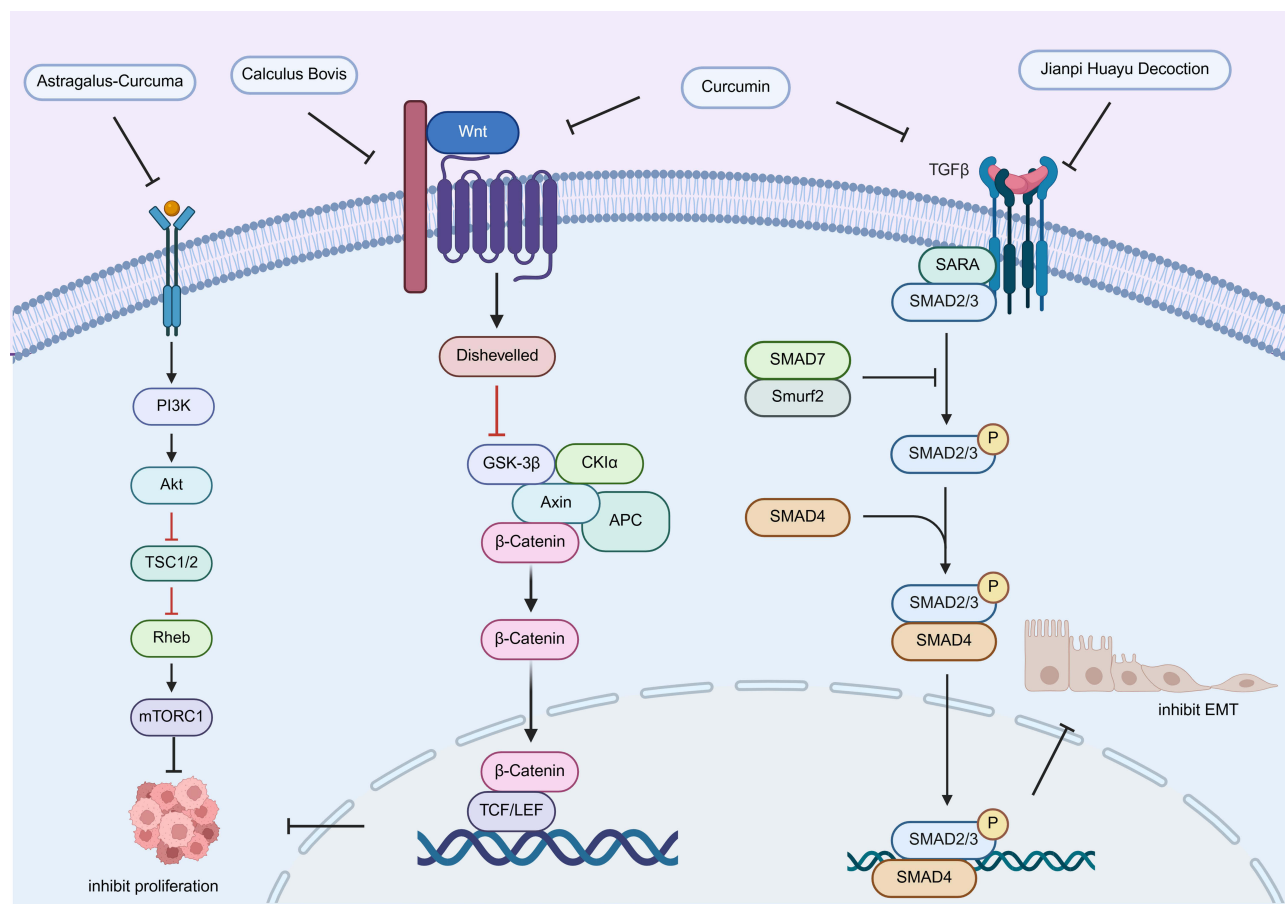
Regulation of signaling pathways is an effective way to inhibit HCC. Bufalin has been an inhibitor of the CCRK-driven  $\beta$ -catenin/TCF oncogenic signaling pathway and the AKT/GSK3 $\beta$ / $\beta$ -catenin/E-cadherin signaling pathway, positioning it as a promising candidate for anti-HCC treatment.<sup>51,52</sup> Anhydroicaritin, a flavonoid primarily sourced from *Epimedium* plants, is extracted from the roots of *Epimedium brevicornu* Maxim and has exhibited inhibitory effects on HCC. Its active component, AHI, may exert these effects by inhibiting the PI3K/AKT signaling pathway activation.<sup>56</sup> The IL-6 and signal transducer and activator of transcription 3 (STAT3) signaling pathways play a crucial role in the initiation and

progression of HCC. Additionally, *Artemisia capillaris* (AC) has been widely used in treating various hepatic disorders, including HCC. Research indicates that extracts from *Artemisia capillaris* can significantly reduce the proliferation and colony-forming ability of HCC cells. These extracts also inhibit IL-6 activation on STAT3, thereby blocking the synthesis of downstream molecules in both HCC and W4P-NIH3T3 cells. Our findings suggest that AC extracts possess multiple anticancer properties against HCC through the modulation of the IL-6/STAT3 signaling pathway.<sup>76</sup> Furthermore, cantharidin has hindered HCC progression by affecting the JAK2/STAT3 and PI3K/Akt pathways, with this influence being dependent on EphB4.<sup>69</sup>

In summary, despite the compositional differences among various traditional Chinese medicine (TCM) extracts and compound prescriptions, their anti-liver cancer effects often achieve synergistic intervention through common signaling pathways and molecular targets. For instance, key pathways such as PI3K/AKT, Wnt/ $\beta$ -catenin, and TGF- $\beta$ /SMAD are repeatedly regulated in the mechanisms of multiple TCMs, indicating that TCM exhibits the characteristics of multi-target and multi-pathway integrated action in the process of anti-liver cancer. Figure 4 can assist in understanding this characteristic of the mechanism of action of TCM.

## Clinical Evidence and Applications of Herbal Extracts and Formulas in HCC Treatment

Beyond robust preclinical evidence that elucidate its mechanisms, the clinical value of TCM in HCC management is supported by a growing body of observational and interventional studies. This section reviews the clinical evidence for



**Figure 4** Astragalus–Curcuma, Calculus Bovis, curcumin, and Jianpi Huayu Decoction regulate the PI3K/Akt/mTOR, Wnt/ $\beta$ -catenin, and TGF- $\beta$ /SMAD signaling pathways. These interventions suppress mTORC1 activity, promote  $\beta$ -catenin degradation, and inhibit TGF- $\beta$ -induced SMAD2/3 activation, thereby inhibiting cell proliferation and epithelial–mesenchymal transition (EMT).

TCM as both a standalone therapy and an integrative therapy, highlighting its role to improve survival outcomes, alleviate symptoms, and enhance the efficacy of conventional treatments.

In Table 4, we summarize the clinical evidence regarding the use of traditional Chinese medicine in the treatment of hepatocellular carcinoma.

## Clinical Evidence and Application of a Single Herbal Extract and Formula in Hepatic Carcinoma Treatment

The core advantage of TCM in treating tumors is “syndrome differentiation and treatment”. It comprehensively analyzes the causes, locations, and nature of tumors according to the patient’s specific condition, constitution, and external environmental factors.<sup>126</sup> From a holistic perspective, TCM aims to harmonize the body’s yin and yang, qi, blood, and body fluids, as well as organ functions, thereby restoring the body to its optimal state and creating an internal environment unsuitable for tumor growth and development, striving for fundamental tumor treatment. TCM brings multiple benefits to patients with liver cancer, alleviating pain, reducing complications (eg, jaundice, ascites), improving symptoms (eg, nausea, vomiting, loss of appetite), and regulating emotions, thereby enhancing quality of life. Conversely, it strengthens the righteous qi, enhances physical fitness, boosts immunity, and reduces the toxic side effects of chemotherapy and radiotherapy, thereby synergizing with these treatments while helping to inhibit tumor recurrence and metastasis. It is suitable for adjuvant treatment postoperatively for early-stage liver cancer and for patients in the mid-to-late stages who cannot tolerate surgery or chemotherapy, helping to alleviate symptoms, control disease, and prolong survival.

Despite numerous clinical observations and retrospective studies indicating that TCM may be beneficial in the treatment of HCC, the quality and robustness of the existing evidence necessitate thorough evaluation. This section will systematically review the clinical evidence on TCM and, based on this review, will conduct a critical analysis of its study design, potential biases, and the external validity of these conclusions, with the aim of providing readers with a balanced perspective on the current state of TCM clinical evidence.

Liao et al conducted a retrospective cohort study involving 127,237 patients newly diagnosed with liver cancer, among whom 30,992 (24.36%) received TCM treatment. Further analysis revealed that the average follow-up duration was 5.67 years (standard deviation, 1.47) for TCM users and 5.49 years (standard deviation, 3.64) for non-TCM users. After multivariate adjustment, patients who received TCM demonstrated a notable decrease in mortality risk compared with those who did not employ TCM, indicated by a hazard ratio (HR) of 0.65 alongside a 95% confidence interval (CI) of 0.64–0.66. Furthermore, within various subgroups of chronic liver disease, TCM exhibited consistent and significant protective benefits. In particular, among the array of TCMs investigated, Jiawei Xiaoyao San and Chaihu Shugan Decoction exhibited relatively pronounced efficacy in improving patient survival rates.<sup>123</sup>

Liu et al included 3483 patients with HCC and employed the Cox proportional hazards regression model to quantify the HR and related mortality risk of TCM treatment in patients with HCC. Meanwhile, they employed the Kaplan–Meier survival analysis method to plot survival curves, visually presenting patient survival status and validating the role of TCM treatment in prolonging survival time in patients with HCC through Log rank tests. The findings indicated that Cox multivariate analysis identified TCM treatment as an independent protective factor associated with five-year survival in patients with HCC, with an adjusted HR of 0.46 and a 95% CI of 0.40–0.52 ( $p < 0.0001$ ). Further, Kaplan–Meier survival curves revealed that, after propensity score matching, both overall survival (OS) rates and progression-free survival (PFS) rates were significantly higher in individuals receiving TCM than in those who did not.<sup>124</sup> In a separate study conducted by Liao et al, 1339 patients with HCC who received TCM as an adjuvant therapy were compared with 13,390 patients who only received Western medicine. This study employed the Kaplan–Meier method alongside the Cox proportional hazards model to evaluate the relative risk of death between the two patient groups. The results demonstrated that patients with HCC who received TCM adjuvant therapy had a significantly lower relative risk of death compared with those undergoing only Western medicine treatment.<sup>125</sup> Overall, TCM adjuvant treatment appears to play a beneficial and effective role in enhancing the survival rates of patients with liver cancer.

**Table 4** Summary of Key Clinical Studies on TCM Interventions for HCC

Study (Author, Year)	Study Design	Patient Population/Sample Size (n)	TCM Intervention	Control/ Comparison Group	Main Outcomes
Liao et al, 2015 <sup>123</sup>	Retrospective cohort study	Newly diagnosed liver cancer (TCM: 30,992; Non-TCM: 96,245)	Various TCM prescriptions	No TCM	Lower mortality risk (HR=0.65, 95% CI: 0.64–0.66).
Liu et al, 2019 <sup>124</sup>	Retrospective cohort study	HCC (Total: 3483)	Adjuvant TCM therapy	No adjuvant TCM	Improved 5-year survival (HR=0.46, 95% CI: 0.40–0.52).
Liao et al, 2020 <sup>125</sup>	Retrospective cohort study	HCC (TCM+WM: 1339; WM: 13,390)	Adjuvant TCM + WM	WM only	Reduced risk of death.
Zhong et al, 2014 <sup>15</sup>	Randomized Controlled Trial (RCT)	Post-hepatectomy HCC (n=60 each group)	Hepatectomy + Jianpi Huayu Therapy	Hepatectomy alone	Improved DFS (28.7 vs 22.6 months) and OS rates.
Li et al, 2025 <sup>12</sup>	Prospective cohort study	Unresectable HCC (Exposed: 48; Non-exposed: 44)	Targeted+Immuno + Huaier Granules	Targeted+Immuno only	Longer mPFS (8.9 vs 5.0 months, HR=0.50); higher response rate.
Jia et al, 2020 <sup>13</sup>	Meta-analysis	Advanced HCC	TACE + Jinlong Capsule (JLC)	TACE alone	Improved OS, response rates, liver function and reduced side effects.

The large-scale retrospective cohort analyses by Liao et al and Liu et al showed that the mortality risk of HCC patients receiving TCM-assisted treatment was significantly reduced (hazard ratios [HRs] of 0.65 and 0.46, respectively). This large-scale real-world evidence provides important epidemiological clues for the potential survival benefits of TCM. However, inherent limitations exist in retrospective study designs. For example, study results may be affected by confounding bias. Despite multivariable adjustments, there may be unmeasured systematic differences in baseline characteristics (such as performance status, patient compliance, socioeconomic factors, and details of concurrent therapies) between TCM users and non-users, which may partially explain the survival differences. Additionally, there is heterogeneity in TCM, as it encompasses various formulations, doses, and treatment durations, complicating the attribution of treatment effects. Furthermore, there are limitations in causal inference; such studies can establish correlations but find it difficult to confirm causality. Therefore, these findings should be viewed as hypothesis-generating rather than confirmatory conclusions.

## Impact of Combined TCM and Modern Medical Technologies on the Prognosis of Patients with Liver Cancer

The integration of TCM with conventional therapies, such as surgery, chemotherapy, and radiotherapy, provides several benefits for patients with liver cancer.<sup>127,128</sup> Research reveals that this combined approach leads to better survival rates and a lower risk of mortality. TCM plays a crucial role in inhibiting cancer cell growth, promoting programmed cell death (apoptosis), preventing new blood vessel formation (angiogenesis), slowing down tumor progression, and decreasing recurrence chances. Further, it improves the effectiveness of conventional treatments. TCM also helps alleviate various symptoms and side effects that patients with liver cancer frequently experience, such as pain, fatigue, nausea, and vomiting. TCM improves patients' overall quality of life by mitigating the toxic effects associated with conventional therapies. Moreover, it popularly strengthens the immune system, supports liver function recovery, reduces psychological stress, and promotes better mental health. These benefits contribute to a holistic treatment approach that addresses multiple pathways and mechanisms. A crucial feature of TCM is its emphasis on individualized treatment, where personalized plans are developed based on each patient's unique situation. This tailored approach enables more precise regulation of immune function, metabolism, and other physiological aspects, causing better treatment outcomes. Overall, this comprehensive treatment strategy not only improves survival rates but also significantly promotes the quality of life of patients with liver cancer, thereby contributing positively to their overall health and well-being.

Zhang et al analyzed a group of patients diagnosed with unresectable HCC who had received treatment at two different medical facilities from March 2022 to July 2023. These patients were treated with targeted therapy and immunotherapy, with one group receiving Huai'er granules, referred to as the exposed cohort, whereas the other group, which did not receive these granules, was designated as the nonexposed cohort. The results revealed that the median PFS (mPFS) for the exposed cohort was 8.9 months, which was significantly longer than the 5 months recorded for the nonexposed cohort. This difference was statistically significant ( $P = 0.001$ ), with an HR of 0.50, indicating that those in the exposed cohort had a 50% lower risk of disease progression. Further analysis revealed that the 6-month PFS rates were 66.7% for the exposed cohort compared to 34.1% for the nonexposed cohort, again demonstrating a significant statistical difference ( $P = 0.001$ ). Regarding clinical effectiveness, as identified by TCM symptom classification, the clinical efficacy rate for the exposed group was 87.50%, markedly exceeding the 59.09% rate of the nonexposed group ( $P = 0.001$ ). Moreover, an improvement in fatigue levels was significantly noted in the exposed cohort post-treatment ( $P = 0.023$ ). Importantly, extrahepatic metastasis appeared as an independent adverse prognostic factor, whereas Huai'er granule administration was associated with a substantial 47% reduction in the risk of disease progression.<sup>12</sup>

Zhong et al randomly assigned a cohort of 120 patients diagnosed with HCC to two distinct groups: one receiving liver resection in conjunction with "Jianpi Huayu Therapy" (treatment group,  $n = 60$ ) and the other undergoing liver resection alone (control group,  $n = 60$ ). Recurrence was observed in 104 patients throughout the follow-up period. The treatment group's disease-free survival (DFS) rates at 1, 3, and 5 years, along with the median DFS, were recorded at 78.2%, 29.2%, 14.3%, and 28.7 months, respectively. In contrast, the control group demonstrated DFS rates of 75.0%, 23.3%, and 6.4%, and a median DFS of 22.6 months. A total of 101 fatalities were documented, with the treatment

group's survival rates at 1, 3, and 5 years of 98.3%, 78.0%, and 43.6%, respectively, and an average survival duration of 52.6 months, whereas the control group demonstrated corresponding rates of 96.7%, 74.7%, and 37.4%, respectively, and an average survival time of 49.8 months. This investigation indicates that the integration of "Jianpi Huayu Therapy" with liver resection significantly mitigates postoperative recurrence and metastasis among patients with HCC, thereby improving both DFS and OS.<sup>15</sup> Additional studies have revealed that when compared with conventional transarterial chemoembolization (TACE) alone, the combination of TACE with JLC notably prolongs the total survival duration of patients, ranging from 6 to 36 months ( $p < 0.05$ ). Furthermore, the overall response rate among patients improved significantly, along with a markedly increased disease control rate. Moreover, the patients exhibited considerable enhancements in liver functionality, quality of life, and immune competence, whereas the adverse effects associated with TACE were effectively alleviated after the combined treatment approach.<sup>13</sup>

Although the above clinical observations provide preliminary support for the efficacy of traditional Chinese medicine, these findings must be viewed with caution and the level of evidence carefully evaluated. Currently, most clinical data are derived from observational studies (such as cohort studies, case-control studies) or retrospective analyses, which are inherently susceptible to confounding factors, recall bias, and selection bias. For instance, many studies failed to fully control for confounding variables such as patients' concomitant medications and lifestyle factors. According to the evidence classification system of evidence-based medicine, well-designed randomized controlled trials (RCTs) and their systematic reviews are regarded as the highest level (I grade/A grade) evidence, while case-control studies and cohort studies typically belong to lower levels (such as II-2 grade or III-B grade evidence). The majority of clinical studies cited in this review fall into this category, and their conclusions mainly suggest potential associations rather than conclusive causal relationships. Moreover, many clinical trials have small sample sizes, short follow-up periods, and lack multi-center, large-sample RCTs that serve as the gold standard for verification. Therefore, the current clinical evidence base still needs to be consolidated through more rigorous designs. There is an urgent need for future research to conduct high-quality, large-sample RCTs to elevate the evidence level of traditional Chinese medicine treatment for HCC from the current "moderate" (B grade) or "expert opinion" (D grade) level to the "good" (A grade) scientific recommendation level.

## Discussion

In HCC treatment, TCM extracts and formulas demonstrate distinct biological mechanisms and hold significant potential for clinical application. These treatments affect various processes, such as cell proliferation, apoptosis, migration, and the tumor microenvironment, thereby providing innovative approaches to HCC management. Furthermore, this research provides fresh insights into the integration of traditional and modern medical practices. Existing clinical evidence supports the beneficial effects of TCM in HCC treatment; however, current studies have notable limitations. These involve an incomplete understanding of the mechanisms behind certain herbal components, small sample sizes in clinical trials, and a scarcity of large-scale randomized controlled trials. Furthermore, while the mechanistic data are compelling, a significant portion originates from reductionist *in vitro* models using high, sometimes non-physiological, concentrations of single compounds. The extrapolation of these findings to the complex pharmacokinetics and synergistic effects of whole herbal formulas in humans requires caution. The reliability of individual studies varies; studies employing multiple methodological approaches (eg, genetic knockdown, specific inhibitors, *in vivo* validation) provide stronger evidence than those relying solely on phenotypic observations and correlative protein expression changes.

In exploring the potential of TCM for HCC treatment, it is imperative to address the critical challenges of standardization and safety. The concentrations of active ingredients, bioavailability, and batch-to-batch consistency of TCM extracts and formulas cited in current research often lack rigorous standardization, which can result in variations in efficacy and challenges in reproducing results. Furthermore, factors such as herbal origins, cultivation conditions, processing methods, and potential contaminants (eg, heavy metals, pesticide residues) and adulterants can impact product quality and safety. Although numerous clinical studies suggest that adjuvant TCM therapy can improve prognosis with good tolerability, potential risks such as hepatotoxicity or interactions with modern targeted and immunotherapeutic agents should be carefully considered. Future research and practice should aim to establish stricter quality control standards for TCM, promote the identification and standardized preparation of active components, and systematically

monitor and report adverse events in large-scale clinical trials. By integrating TCM with modern medicine under a more regulated and controlled framework, its synergistic value in treating HCC can be realized more safely and effectively.

Translating insights from TCM into modern drug development and therapy design is a crucial approach for advancing HCC treatment. Historically, the isolation of artemisinin from *Artemisia annua*, now a first-line antimalarial, exemplifies the vast potential of discovering novel active compounds from traditional materia medica. For HCC, contemporary research is elucidating the specific targets and signaling pathways (eg, EGFR/AKT/mTOR, PI3K/AKT) of certain TCM extracts (eg, curcumin, cinobufacini) and formulations (eg, the *Astragalus–Curcumae* herb pair).<sup>23,29,38</sup> Such mechanistic studies not only provide a scientific basis for the current clinical use of TCM but also reveal novel therapeutic targets and offer clues for designing new small-molecule drugs or biological agents. The inherent multi-component, multi-target nature of TCM aligns well with modern concepts of polypharmacology and network pharmacology.<sup>17,19,20</sup> Utilizing systems biology approaches to decipher the action networks of TCM formulas can facilitate the development of synergistic drug combinations tailored to the complex pathological environment of HCC. Regarding clinical strategy, the combination of TCM with existing therapies (eg, targeted therapy, immune checkpoint inhibitors, TACE) has shown the potential to improve patient prognosis.<sup>12,13,15</sup> Future integrative research must address hurdles such as the standardization of TCM products and the evaluation of drug interactions. Through well-designed prospective clinical trials, the value of TCM as an adjuvant or synergistic therapy to enhance efficacy and reduce adverse effects can be validated, thereby catalyzing the development of next-generation HCC treatment regimens inspired by TCM wisdom.

Future research is recommended to explore deeper into the mechanisms underlying TCM, refine herbal formulas and preparations, and conduct large-scale clinical trials to enhance the practical application of TCM in HCC treatment. Further, studies should prioritize the integration of TCM with modern medicine, investigating how both can work together to treat HCC more effectively. Treatment outcomes and the quality of life of patients can be significantly improved by systematically assessing the various mechanisms through which TCM affects HCC and its combined use with contemporary treatment methods. Furthermore, adopting more standardized clinical trial designs will be crucial for increasing the reliability and reproducibility of the findings, ultimately fostering greater acceptance of TCM in HCC management.

In conclusion, TCM presents considerable promise in HCC treatment. However, further research and clinical trials are crucial to validate its effectiveness and safety, which would lead to more comprehensive and personalized treatment options for patients with HCC.

## Conclusion

This review synthesizes evidence showing that these extracts and formulas exert anti-HCC effects through multi-targeted biological mechanisms. These include the induction of apoptosis and ferroptosis; inhibition of proliferation, migration, EMT, and angiogenesis; as well as modulation of immune responses and key oncogenic signaling pathways. These multifaceted effects align with the holistic principle of TCM and highlight its potential role as a synergistic agent in cancer therapy.

Clinical studies indicate that Traditional Chinese Medicine may improve survival and quality of life in patients with hepatocellular carcinoma, particularly when combined with conventional therapies such as surgery, transarterial chemoembolization, and systemic treatments. However, the available evidence remains largely observational and of limited methodological strength, thereby restricting its broader clinical application. To advance this field, priority should be given to the conduct of large-scale, well-designed randomized controlled trials that can provide high-quality evidence on the efficacy and safety of standardized TCM protocols.

From a drug discovery perspective, TCM can serve as both a source of novel bioactive compounds and provide insights into multi-target therapeutic strategies. Modern methodologies such as network pharmacology and integrated multi-omics analyses are essential for elucidating the complex mechanisms of herbal formulations and guiding the rational design of TCM-inspired combination therapies.

Before TCM can be widely integrated into clinical practice, several challenges must be systematically addressed. These include establishing consistent quality standards for TCM products, conducting comprehensive safety evaluations and systematically monitoring herb-drug interactions, and refining clinical trial methodologies to enhance study validity and reproducibility.

In summary, TCM holds significant promise as a complementary approach in hepatocellular carcinoma management. Future efforts should focus on translating preclinical findings into clinically validated outcomes through interdisciplinary collaboration, stringent quality control, and methodologically rigorous clinical research. A coordinated approach will be necessary to fully realize the therapeutic potential of TCM and achieve measurable improvements in patient outcomes.

## Abbreviations

AC, *Artemisia capillaris*; ACHP, The Astragalus–Curcumae herb pair; AKT, Protein Kinase B; CI, Confidence interval; COX-2, Cyclooxygenase-2; DFS, Disease-free survival; EGFR, Epidermal Growth Factor Receptor; EMT, Epithelial-mesenchymal transition; FZP, The Yangyin Fuzheng Jiedu prescription; FZQJ, Fuzheng Qingjie; G-CSF, Granulocyte Colony-Stimulating Factor; GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; GSH, Glutathione; HBV, Hepatitis B virus; HCC, Hepatocellular carcinoma; HQF, The Huqi formula; HR, Hazard ratio; HUVECs, Human umbilical vein endothelial cells; MDSCs, Myeloid-derived suppressor cells; mPFS, Median PFS; mTOR, Mammalian Target of Rapamycin; mTORC1, Mechanistic Target of Rapamycin Complex 1; NF- $\kappa$ B, Nuclear Factor Kappa B; NOD1, Nucleotide-binding Oligomerization Domain-containing protein 1; OP-B, Ophiopogonin-B; OS, Overall survival; PD-1, Programmed cell death protein1; PFS, Progression-free survival; PI3K, Phosphatidylinositol 3-Kinase; PPL, Polyphyllin I; RCT, Randomized controlled trial; ROS, Reactive oxygen species; STAT3, Signal transducer and activator of transcription 3; TACE, Transarterial chemoembolization; TCM, Traditional Chinese medicine; TGF $\beta$ , Transforming Growth Factor Beta; TNF- $\alpha$ , Tumor necrosis factor-alpha; VEGF-A, Vascular endothelial growth factor A; VEGFR-2, Vascular endothelial growth factor receptor 2; WM, Western medicine; YGJDSJ, Yanggan Jiedu Sanjie.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

There is no funding to report.

## Disclosure

The authors report no conflicts of interest in this work.

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