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REVIEW

Traditional Chinese Medicine as a Tool for the Treatment of Hepatocellular Carcinoma by Targeting Pathophysiological Mechanism

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Abstract: Liver cancer is a significant global health concern, with projections indicating that the incidence of morbidity may surpass one million cases by 2025. Hepatocellular carcinoma (HCC) is the predominant subtype of liver cancer, constituting approximately 90% of all liver cancer diagnoses. Infections caused by the hepatitis B virus (HBV) and hepatitis C virus (HCV) are recognized as primary risk factors for the development of HCC. However, non-alcoholic steatohepatitis (NASH), which is often linked to metabolic syndrome or diabetes, is increasingly being recognized as a prevalent risk factor in Western populations. Furthermore, HCC associated with NASH exhibits distinct molecular pathogenesis. Patients diagnosed with HCC have access to a range of therapeutic interventions, including liver transplantation, surgical resection, percutaneous ablation, radiation therapy, and transarterial and systemic therapies. Consequently, effective clinical decision-making requires a multidisciplinary approach to adapt individualized treatment plans based on the patient's tumor stage, liver function, and overall performance status. The approval of new first- and second-line pharmacological agents, along with the establishment of immune checkpoint inhibitor therapies as standard treatment modalities, has contributed to an improved prognosis for patients with HCC. Nevertheless, the optimal sequencing of these therapeutic agents remains to be elucidated, highlighting the urgent need for predictive biomarkers to inform treatment selections. Traditional Chinese Medicine (TCM) has demonstrated potential as a complementary and alternative therapeutic approach for liver cancer, warranting further investigation. This review aimed to examine the comprehensive treatment of HCC through the lens of TCM, informed by the current understanding of its epidemiology, diagnosis, and pathophysiology.

Keywords: hepatocellular carcinoma, HCC, Wnt signaling pathway, TCM

Introduction

Liver cancer represents a significant public health concern, with its global incidence on the rise.[1,2] Projections indicate that by 2025, over one million individuals will be diagnosed with liver cancer annually.[3] Hepatocellular carcinoma (HCC) is the predominant subtype, constituting approximately 90% of all liver cancer cases. Hepatitis B virus (HBV) infection is recognized as the primary risk factor for HCC and is responsible for 50% of HCC cases.[4] The risk associated with hepatitis C virus (HCV) infection can be markedly diminished through sustained virological response (SVR) achieved through antiviral therapy.[5] However, individuals with cirrhosis remain at an elevated risk of HCC, even after the successful clearance of HCV. Furthermore, non-alcoholic steatohepatitis (NASH), particularly in conjunction with metabolic syndrome or diabetes, is increasingly recognized as the fastest-growing contributor to HCC, especially in Western countries.[6] Additionally, studies on mutational profiles have implicated aristolochic acid and tobacco as potential cofactors in the etiology of HCC.[7]

The mechanisms underlying morbidity in HCC are diverse and influenced by genotoxic injuries and various etiological factors. Although progress has been made in the academic understanding of the pathophysiology and determinants of this disease, such insights are yet to be effectively integrated into clinical practice. Proof-of-concept studies face challenges, as approximately 25% of HCC tumors harbor actionable mutations, yet the majority exhibit an incidence of less than 10%.[7,8] Recent advancements in the understanding of HCC pathogenesis have illuminated the

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significance of the tumor microenvironment, particularly the roles of the immune system and platelet activation in the pathophysiology of the disease.[9,10] Traditional Chinese Medicine (TCM), a component of complementary and alternative medicine, has demonstrated efficacy in the management of HCC. Its mechanisms of action include inhibition of tumor cell proliferation and growth, induction of apoptosis and autophagy, suppression of metastasis and angiogenesis, and immune modulation. Consequently, this study aimed to investigate the application of TCM in the treatment of HCC based on the pathophysiological understanding of the disease.

Epidemiology of HCC

Liver cancer is the sixth most prevalent cancer globally, with 841,080 new diagnoses reported in 2018, and constitutes the fourth leading cause of cancer-related mortality worldwide.[11] The incidence and mortality rates of HCC are particularly elevated in East Asia and Africa; however, there is a notable increase in cases across various regions in Europe and the United States.[12] Indeed, since the early 2000s, HCC has emerged as the most rapidly increasing cause of cancer-related deaths in the United States, as documented by the Surveillance, Epidemiology, and End Results (SEER) program. If this trend persists, projections indicate that HCC may become the third leading cause of cancer-related mortality by 2030.[13]

In 2020, approximately 906,000 individuals were diagnosed with liver cancer globally, with HCC being the most prevalent subtype.[14] The correlation between morbidity and mortality rates underscores the unfavorable prognosis associated with this condition.[15] The incidence of HCC varies significantly across different geographic regions and ethnic groups, which is primarily attributable to the distribution of key risk factors. The majority of HCC patients present with a history of chronic liver disease, which may stem from chronic infections with HBV or HCV, alcohol consumption, alcoholic steatohepatitis (ASH), nonalcoholic fatty liver disease (NAFLD), or NASH. Additional factors such as obesity, diabetes, and tobacco use are also linked to an elevated risk of HCC, as well as rarer conditions, such as hemochromatosis and genetic tyrosinemia type 1.[16] The global prevalence of HCC risk factors is heterogeneous, with HBV being more common in Asia, HCV in Japan, and NAFLD and NASH in Europe and North America, along with alcohol-related risks. In many instances, the development of HCC is influenced by a combination of factors, including demographic characteristics, severity and activity of the underlying liver disease, metabolic conditions, and lifestyle choices. Since the early 2000s, there has been a global decline in the incidence of malignancies linked to viral hepatitis, which is attributed to the introduction of neonatal HBV vaccination programs and the availability of highly effective antiviral treatments for both HBV and HCV.

Although the prevalence of viral HCC has declined, there has been a notable increase in the incidence of liver cancer associated with NAFLD and NASH.[17] Currently, NAFLD is the most prevalent chronic liver disease, with a global incidence of approximately 25% (14% in Africa, 32% in the Middle East, and 25% in Europe and the United States).[18] It is crucial to emphasize the importance of optimizing both glycemic control and body weight as these factors are independently associated with an elevated risk of liver cancer. However, prospective studies have not yet established the risk of HCC in individuals diagnosed with NAFLD and NASH.[19,20] Furthermore, genetic variants in patatin-like phospholipase domain containing 3 (PNPLA3; rs738409), transmembrane 6 superfamily member 2 (TM6SF2; rs58542926), and hydroxysteroid 17-beta dehydrogenase 13 (HSD17B13) have been associated with the development of HCC in individuals with NAFLD and NASH, as well as in those with alcoholic liver disease.[21,22] While alcohol-related liver disease is more prevalent among men, women exhibit a higher relative risk of developing HCC than their male counterparts. A meta-analysis conducted in 2017 indicated that the daily consumption of two cups of coffee was associated with a 35% reduction in the risk of HCC.[23]

Genetics of HCC

Numerous investigations in the fields of genomics, epigenomics, histopathology, and immunological analysis have contributed to the establishment of molecular and immunological classification systems for HCC.[24] The molecular classification of HCC is delineated based on the principal molecular drivers and their corresponding pathways,[25–27] or alternatively, based on the immune status of the tumor.[28] These molecular classifications are correlated with specific genomic abnormalities, histopathological characteristics, and clinical outcomes. The proliferative class constitutes

approximately 50% of HCC cases and is typically characterized by a high prevalence of TP53 mutations and amplifications of FGF19 or CCND1, which are predominantly observed in HCCs associated with HBV and are associated with the poorest prognosis. The proliferative class is further divided into two subclasses: proliferation-progenitor group and proliferation-Wnt-TGFβ group. The proliferation-progenitor subgroup represents 25–30% of HCC cases[25] and is marked by the activation of classical cell proliferation pathways, including the PI3K-AKT-mTOR signaling pathway, RAS-MAPK pathway, and MET and IGF signaling cascades.[29] This subgroup also exhibits the expression of progenitor markers such as EPCAM and alpha-fetoprotein, which are closely linked to cancer genome mapping, as outlined by The Cancer Genome Atlas (TCGA).[26] Conversely, the proliferation-WNT-TGFβ group, which accounts for 20% of HCC cases, is characterized by atypical Wnt activation and is associated with Group 3 of TCGA. In contrast, the non-proliferative tumor group comprised the remaining 50% of HCC cases,[26] exhibiting a more favorable prognosis and correlating with group 2 of TCGA. Within the nonproliferative category, at least two distinct subgroups have been identified: one characterized by the predominance of typical Wnt signaling associated with CTNNB1 mutations and the other characterized by the activation of IFNα signaling.[30]

A report detailing the classification of HCC based on immune cell status has significantly enhanced our understanding of the molecular features associated with HCC.[28] This classification system offers supplementary insights derived from immune characteristics, categorizing HCC tumors into distinct subtypes: immunologically active, depleted, intermediate, and rejected. Within the immune class, there are two subclasses: the immunocompetent subclass and the immunodepleted subclass, which are distinguished by the varying nature of immune cell infiltration. Immunologically active HCC tumors, which account for approximately 20% of cases, exhibit a predominance of active helper T cells ($CD4^+$ cell infiltrates) and cytotoxic T cells ($CD8^+$ cell infiltrates), and demonstrate responsiveness to immune checkpoint inhibitors (ICIs). Conversely, immunodepleted tumors are characterized by a reduction in the number of TGFβ-driven $CD8^+$ cells. At the opposite end of the spectrum, immunorejecting tumors are characterized by low levels of T-cell infiltration, an increase in regulatory T cells (T_{reg}), and a dominance of classical Wnt signaling pathways along with other immunosuppressive mechanisms. Tumors classified as immune rejection are generally resistant to treatment with ICIs.[31]

Pathophysiology of HCC

The pathophysiology of HCC is characterized by a complex, multistep process involving the interaction of various factors during the initial stages of malignant hepatocyte transformation and subsequent HCC development. These factors include genetic predisposition, interplay of viral and non-viral risk elements, cellular microenvironment, involvement of diverse immune cells, and severity of pre-existing chronic liver disease. Notably, alterations in the microenvironment represent a significant facilitating characteristic of cancer, as they play a critical role throughout all phases of malignant progression from the initial transformation to the final stages of carcinogenesis.

Debate persists regarding the cellular origin of HCC. Similar to other cancer types, potential cells of origin may include hepatic stem cells, expanded populations of progenitor cells, or mature hepatocytes. However, the existence and functional role of stem cells in the liver remain controversial. Furthermore, mature hepatocytes, which are long-lived cells, retain a substantial proliferative capacity following injury. Numerous murine models support the hypothesis that HCC may arise from transformed mature hepatocytes; however, there is evidence suggesting that hepatic stem cells could serve as a source of HCC.[32] Interestingly, intrahepatic cholangiocarcinomas and tumors exhibiting mixed HCC or cholangiocarcinomatous characteristics frequently appear to originate from mature hepatocytes, underscoring the concepts of cellular plasticity and heterogeneity. This observation reinforces the notion that the morphological and epigenetic characteristics of tumors do not necessarily correlate with the original cell type from which they derive.[33,34]

High-quality next-generation sequencing enables the identification of cancer driver genes with either oncogenic or tumor-suppressor functions that are recurrently observed in HCC. The most prevalent alteration among these driver genes is telomerase activation due to mutations in the TERT promoter, viral insertions, chromosomal translocations, or gene amplification, which occurs in approximately 80% of HCC cases.[35] Research indicates that the Wnt–β-catenin signaling pathway is activated in 30–50% of cases, primarily due to mutations in CTNNB1 (which encodes β-catenin) or inactivation of AXIN1 or APC, both of which are inhibitors of the Wnt pathway.[7] Other frequent mutations or genetic alterations include TP53, RB1, CCNA2, CCNE1, PTEN, ARID1A, ARID2, RPS6KA3, and NFE2L2, all of which affect

cell cycle regulation. Furthermore, genetic variants associated with epigenetic regulation, oxidative stress, and AKT-mTOR or MAPK signaling pathways have also been implicated in HCC pathogenesis. Recurrent focal chromosomal amplifications of genes such as CCND1, PGF19, VEGFA, MYC, and MET lead to their overexpression, thereby activating various oncogenic signaling pathways, including those mediated by receptor tyrosine kinases.[30] Although cancer driver mutations accumulate in a seemingly random manner, certain genes are linked to specific molecular subclasses of HCC that are delineated by transcriptional profiling and histological characteristics.[36]

Moreover, the influence of risk factors on HCC pathogenesis is well documented. For instance, the toxic effects of aflatoxin B1 are exacerbated by HBV infection, particularly in individuals with null GSTT1 polymorphisms.[37,38]

The predominant locus for insertional mutagenesis induced by HBV is located within the promoter region of the TERT gene, leading to the overexpression of telomerase.[39] The activation of telomerase inhibits the natural degradation of chromosomes that occurs with each cell division as a consequence of aging. Aberrant activation of telomerase safeguards cells from senescence and facilitates cellular transformation.[40] Additionally, other frequently inserted genes associated with HBV have been identified as potent oncogenes that activate cell cycle regulatory genes including CCNA2 and CCNE1. These oncogenic alterations can induce replication stress and complex genomic rearrangements.[41] In a limited cohort of patients with HCC, adeno-associated virus type 2 has been observed to exhibits analogous insertional oncogenic mutations, particularly at common viral insertion hotspots within the TERT promoter, CCNA2, and CCNE1. These findings imply that specific oncogenes activated by viral infection may serve as early drivers of hepatocyte transformation. Conversely, HCV infection does not exhibit a pronounced direct carcinogenic effect; rather, the induced mutations are attributed to oxidative stress resulting from chronic inflammation.

Obesity is associated with an elevated risk of cancer in various organ systems.[42] It can induce systemic alterations, including modifications in the immune function and endocrine systems, which are commonly observed in numerous cancer types. Recent findings indicate that fatty liver disease is rapidly emerging as the predominant cause of HCC in Western countries.[43] Research has elucidated that the liver-specific mechanisms through which NAFLD or NASH fosters HCC include metabolic and oxidative stress, dysregulated immune responses, pathological inflammation, and disrupted endocrine and adipokine signaling pathways.[44] Hepatocytes experience oxidative and endoplasmic reticulum (ER) stress due to excess fatty acids, which can lead to pathological inflammation and pancreatic cancer.[19] One study highlighted the pathogenic role of ER stress in NASH-related HCC in murine models, demonstrating that ER stress in hepatocytes activates inflammatory signaling pathways, particularly nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and tumor necrosis factor (TNF), thereby promoting HCC development.[45] However, these pathogenic mechanisms have yet to be validated in human HCC cases. DNA damage[46] may arise from disruptions in fatty acid metabolism within hepatocytes, which is attributed to increased production of reactive oxygen species (ROS) stemming from mitochondrial dysfunction. Furthermore, the decline in specific metabolic enzymes due to mitochondrial impairment compromises the capacity of hepatocytes to repair DNA damage.[47] Metabolic dysfunction also causes alterations in inflammatory signaling pathways.[48] In the context of NASH, lipid production may not only be augmented, but also modified to yield more pathogenic lipids that function as metabolites.[49,50] Similarly, disruptions in cholesterol metabolism may contribute to the morbidity associated with HCC,[50] potentially through the generation of tumor-promoting ligands for nuclear receptors. Although autophagy is recognized for its anti-tumor properties, research has indicated that lipophagy plays a significant role in the morbidity mechanisms of HCC. Overexpression of sequestosome 1, a regulator of lipophagy, has been correlated with HCC in hepatocytes from NASH patients and in murine models.[51]

The infiltration of immune cells within fatty liver tissue is a histopathological characteristic indicative of NASH.[9] Establishment of animal models that accurately mimic human HCC is crucial for both fundamental and translational research aimed at elucidating the mechanisms underlying morbidity associated with this condition.[52,53] Various experimental models have indicated that immune cells and cytokines significantly contribute to the pathophysiological mechanisms of HCC. For instance, in a murine model, chronic NAFLD activated $CD8^+$ T cells, resulting in hepatocyte damage that ultimately led to HCC development.[54] Furthermore, NAFLD is associated with selective depletion of intrahepatic $CD4^+$ T cells, which are essential for initiating an effective anti-tumor adaptive immune response.[55] Other immune cell populations, including B cells, regulatory T cells, natural killer cells, and various bone marrow-derived cells, have also been implicated in morbidity mechanisms associated with NASH-induced HCC.[44] Notably, consistent with

clinical findings,[56] the recruitment and activation of platelets in the context of NASH contributes to HCC development in murine models, particularly through signaling via platelet glycoprotein Ibα (GPIbα), indicating potential therapeutic avenues.[57] Additionally, alterations in the cytokine environment have been demonstrated to play a pathogenic role in the relationship between NASH and HCC.[10] For example, research has revealed that NASH is characterized by the overexpression of hepatic interleukin-6 (IL-6) and TNF, both of which are known to drive HCC in various etiological contexts, including NASH.[58] Collectively, these mechanisms may concurrently facilitate the progression of HCC in the setting of fatty liver disease; however, their relative contributions to human HCC remain unclear. Analyzing the mutational profiles of NASH-associated HCC in comparison with HCC arising from other etiologies may provide insights into the relative significance of these various factors.

The involvement of circadian dysregulation in the progression of NAFLD to HCC is intricate and multifaceted.[59,60] The primary mechanisms underlying this progression include metabolic disturbances, genomic instability, and aberrant immune regulation.[60] Experimental evidence indicates that irregularities in cell cycle regulation during the G2/M phase significantly expedite hepatocarcinogenesis in CLOCK mutant mice and CRY1/2 double-knockout models, implying that circadian genes play a role in tumor suppression by preserving cell cycle checkpoint functionality.[61] At the metabolic level, disruptions in circadian rhythms markedly affect hepatic lipid metabolic pathways.[60] Transcriptomic analyses have revealed that over 60% of the genes associated with hepatic lipid metabolism are regulated by the circadian clock, including critical components such as fatty acid synthase (FASN) and peroxisome proliferator-activated receptor gamma (PPARγ).[62] In a mouse model exhibiting chronic circadian rhythm disturbances, there was a 2.3-fold increase in liver triglyceride levels compared with the control group, along with a 40% increase in the insulin resistance index, which directly facilitated the transition from NAFLD to NASH.[63,64] From a molecular perspective, dysfunction of the BMAL1/CLOCK complex serves as a central hub in this process.[59] Downregulation of REV-ERBα, which is regulated by this complex, led to a 3.5-fold increase in the expression of the lipid synthesis gene SCD1, a 2.8-fold increase in the secretion of the inflammatory cytokine IL-6, and a 60% decrease in the expression of the DNA repair gene XRCC5. This multifaceted disorder ultimately results in heightened genomic instability within hepatocytes, thereby promoting malignant transformation.[65] Therapeutic strategies targeting circadian rhythms have demonstrated promise.[59] Animal studies have indicated that a timed restriction diet (TRF) can reduce the area of liver steatosis in NAFLD mice by 68% and reduce the incidence of HCC by 54%.[60] In terms of pharmacological interventions, administration of the REV-ERB agonist SR9009 resulted in a 42% reduction in tumor volume, with the underlying mechanism involving restoration of lipid metabolism rhythmicity and enhancement of DNA repair capacity.[66] These findings suggest a novel sequential therapeutic target[60] for the prevention and treatment of NAFLD-HCC.

In recent years, metabolic dysregulation has emerged as a fundamental factor contributing to the pathogenesis of HCC,[67] particularly among high-risk populations such as individuals with obesity, diabetes, and NAFLD, all of which significantly increase the risk of HCC development.[67] The mechanisms underlying HCC morbidity are closely linked to metabolic disorders, with disruptions in bile acid metabolism, cholesterol metabolism, lipid metabolism, and pathways associated with metabolic syndrome serving as critical drivers.[67] Dysregulation of cholesterol metabolism is particularly significant in HCC, as the liver plays a pivotal role in cholesterol homeostasis. Anomalously high cholesterol synthesis can result in lipid accumulation and oxidative stress in the hepatocytes. Research has indicated that the expression of HMGCR, a key rate-limiting enzyme in cholesterol biosynthesis, is upregulated in HCC cells, facilitating cholesterol accumulation, activating the PI3K/Akt/mTOR signaling pathway, promoting cellular proliferation, and inhibiting apoptosis.[68] Furthermore, cholesterol metabolites such as oxysterols can modulate transcription factors such as SREB-1c by interacting with liver X receptors (LXR), thereby enhancing the expression of genes associated with adipogenesis and perpetuating a detrimental cycle.[69,70] Clinical intervention studies have demonstrated that statins can significantly lower the incidence of HCC by inhibiting HMGCR activity, thereby underscoring the pathological relevance of cholesterol metabolism.[67]

The association between bile acid imbalance and HCC has been the subject of extensive investigation in recent years.[71] Dysfunction of bile acid receptors, such as FXR and TGR5, disrupts the synthesis and excretion of bile acids, leading to an excess of secondary bile acids (eg, deoxycholic acid) that promote malignant transformation of hepatocytes via activation of the Wnt/β-catenin signaling pathway. Elevated serum levels of chenodeoxycholic acid (CDCA) in HCC

patients have been shown to induce DNA damage through ROS generation and activate the NF-κB pathway, thereby triggering chronic inflammation.[72] Additionally, aberrantly enhanced de novo lipogenesis (DNL) is a prominent characteristic of metabolically associated HCC.[71] Key lipogenic enzymes such as ACC and ACLY are upregulated in HCC cells, leading to the accumulation of free fatty acids, including palmitic acid. The deubiquitinating enzyme USP22 has been identified as a promoter of ACC and ACLY transcription by stabilizing PPARγ protein, resulting in a two- to three-fold increase in lipid content, a mechanism observed in 60% of HCC samples.[73] Animal studies have shown that USP22 can reduce tumor volume by 70%, whereas PPARγ inhibitors can reverse lipid accumulation and tumor growth. Clinical data analysis indicates that the five-year survival rate for patients exhibiting high USP22 expression is only 28%, which is significantly lower than the 52% survival rate for those with lower USP22 expression.[73]

Insulin resistance and chronic inflammation constitute the microenvironmental foundation for HCC development.[71] Adipose tissue inflammation, driven by obesity, releases cytokines, such as TNF-α and IL-6, which induce insulin resistance in hepatocytes via the JAK/STAT3 pathway, subsequently leading to hyperinsulinemia. Elevated insulin levels activate the IRS-1/PI3K pathway, thereby promoting abnormal hepatocyte proliferation. Research has demonstrated that for every 5 kg/m² increase in body mass index (BMI), the risk of HCC rises by 35%, and the average tumor diameter in HCC patients with diabetes increases by 2.1 cm.[74] Intestinal microbiota also plays a role in HCC progression through various mechanisms. High-fat diets increase intestinal permeability, allowing pathogen-associated molecular patterns, such as lipopolysaccharides (LPS), to enter portal circulation, activate the TLR4/MyD88 pathway in Kupffer cells, and promote the secretion of IL-6 and TGF-β. Clinical cohort studies have revealed that the abundance of ethanol-producing bacteria in the intestines of patients with HCC is three times higher than that in healthy individuals, with their metabolite acetaldehyde capable of directly inducing DNA adduct formation.[67] Fecal microbiota transplantation experiments have confirmed that the microbiota from obese mice can exacerbate liver steatosis in normal mice by fourfold and accelerate the onset of chemically induced HCC.[75]

The metabolic irregularities constitute a multifaceted regulatory network. For instance, the USP22-PPARγ axis plays a significant role in modulating both adipogenesis and inflammation, whereas disorders in bile acid metabolism and alterations in gut microbiota exhibit bidirectional regulation.[71] In light of these mechanisms, preclinical studies have led to the development of small-molecule inhibitors that target USP22 and FXR. Animal model research indicates that the combination of these inhibitors can lead to a 76% %reduction in tumor burden.[73] This evidence underscores the necessity for a multi-target metabolic intervention strategy for future management of HCC.

Pathophysiological Mechanisms of TCM in the Treatment of HCC

In Chinese medical terminology, the term "liver cancer" predominantly refers to HCC[76] unless otherwise specified. TCM does not explicitly define "liver cancer" or "hepatocellular carcinoma" in its classical texts; however, based on the clinical manifestations observed in patients, it can be categorized under the concepts of "fat gas" and "accumulation".[77]

Inhibition of Tumor Cell Proliferation and Growth

TCM exerts a direct inhibitory effect on the proliferation of HCC cells by modulating critical signaling pathways. For instance, extracts derived from Hedyotis diffusa and Scutellaria baicalensis have been shown to inhibit the Wnt/β-catenin signaling pathway, leading to cell cycle arrest at the G0/G1 phase.[78] Additionally, the compound Jiedu Xiaozheng Yin has been demonstrated to impede the self-renewal capacity of cancer stem cells by downregulating the expression of the Bmi1 gene, with experimental results indicating a reduction in tumor volume exceeding 40% in murine models.[79] Furthermore, Coptis chinensis has been found to inhibit the proliferation of HepG2 cells by inducing endoplasmic reticulum stress by activating the NAG-1 gene.[80]

The pathophysiological mechanisms underlying the TCM approach to treating HCC involve a multifaceted regulatory process that targets various pathways. Central to this approach is the aim to restore the internal environmental balance of the body, often referred to as a "holistic view." This strategy seeks to inhibit tumor progression and enhance the host immune response. The following section provides a detailed analysis of the mechanisms involved.

The Induction of Apoptosis and Autophagy Has Been Observed in Various Studies

Matrine has been shown to enhance the apoptosis rate of HepG2 cells threefold, primarily through the upregulation of the pro-apoptotic protein Bax and the downregulation of Bcl-2.[81,82] Additionally, polysaccharides derived from Ganoderma lucidum (GLPS) have been reported to inhibit the PI3K/Akt/mTOR signaling pathway and activate the autophagy-related protein LC3-II, resulting in a reduction in tumor weight by approximately 35% in animal models.[83,84] Furthermore, bufalin has been found to induce the activation of Caspase-3 via the mitochondrial pathway, with clinical data indicating that its use in conjunction with chemotherapy can extend the median survival of patients by 5–9 months.[85]

Inhibition of Metastasis and Angiogenesis

Salvia miltiorrhiza has been shown to reduce the invasive capacity of MHCC97H cells by 60% by suppressing MMP-2 and MMP-9 expression, thereby reducing degradation of the extracellular matrix.[86] Additionally, the Biejiajian Pill modulates the expression of VEGF and TGF-β1, resulting in a 42% reduction in microvessel density in nude mice.[87] Furthermore, Ginsenoside Rg3 inhibits tumor cell adhesion to the vascular endothelium by targeting and obstructing CD44 and integrin αvβ3 signaling pathways.[88]

Immunomodulation

Astragalus polysaccharide (APS) has been shown to significantly enhance the CD4+/CD8+ cell ratio from 0.8 to 1.5, while also promoting the secretion of IFN-γ by a factor of 2.3.[89] Additionally, Paeonia lactiflora and Lycium barbarum have been found to activate dendritic cells via the TLR4/MyD88 signaling pathway, resulting in a 30% reduction in the proportion of Tregs within the tumor microenvironment.[90] Furthermore, clinical studies indicate that the combination of Fuzheng Yiliu granules with interventional therapy can lead to an increase of over 20 points in the Karnofsky Performance Status (KPS) score of patients.[91]

Reversal of Multidrug Resistance

Tetramethylpyrazine enhances the accumulation of doxorubicin in BEL-7402/ADM cells by a factor of four, primarily through the inhibition of P-glycoprotein (P-gp) and multidrug resistance-associated protein 2 (MRP2) expression.[92] Additionally, leech extract has been reported to reduce the IC50 value of 5-fluorouracil (5-FU) in resistant cell lines from 12.5 μM to 3.2 μM,[93] which is attributed to the down-regulation of the NF-κB signaling pathway. Furthermore, quercetin has been shown to restore chemosensitivity by inhibiting the activity of the ATP-binding cassette subfamily G member 2 (ABCG2) transporter.[94]

Regulatory Mechanisms of the Gut-Liver Axis

Recent investigations have demonstrated that Gynostemma pentaphyllum and Poria cocos exert inhibitory effects on the activation of the TLR4/NF-κB signaling pathway. This inhibition is mediated through the modulation of the intestinal microbiota, specifically by increasing the Bacteroidetes/Firmicutes ratio from 0.6 to 1.2, as well as by decreasing endotoxin levels, as evidenced by a 45% reduction in LPS concentrations. Additionally, Paeonol has been shown to decrease the intestinal permeability index, as measured by FITC-dextran, by 60%, while also promoting the release of tumor-associated inflammatory cytokines IL-6 and TNF-α. This effect was attributed to the restoration of ZO-1 protein expression in the intestinal mucosa.

Clinical Practice of TCM in the Treatment of HCC

A randomized controlled trial (RCT) (ChiCTR2400080963) was conducted by Xu Wenjun et al[95] to evaluate the impact of oral administration of the Huqizhengxiao Formula on the survival rate and quality of life of patients diagnosed with stage III hepatitis B-related HCC, characterized by a syndrome of vital qi deficiency, toxin accumulation, and blood stasis following TACE. In this study, 126 patients with stage III hepatitis B-related HCC exhibiting the aforementioned syndrome after TACE were randomly allocated to either the experimental or control group, with 63 participants in each group, maintaining a 1:1 ratio. The control group received symptomatic and supportive treatment through

conventional Western medicine, whereas the experimental group received Huqizhengxiao Decoction in addition to the control treatment. The treatment duration for all participants was 48 weeks, and follow-up assessments were conducted at 4, 8, 12, 24, 36, and 48 weeks. The primary efficacy endpoint was the one-year survival rate, whereas the secondary efficacy endpoints included the Karnofsky performance score and TCM syndrome score. Survival analysis was performed using the Kaplan-Meier method, and the Log rank test was used to compare survival curves between the groups. In conclusion, the findings suggest that oral administration of Huqizhengxiao Formula may enhance the survival rate, extend survival duration, and improve the quality of life of patients with stage III HBV-related HCC who present with a syndrome of vital qi deficiency, toxin accumulation, and blood stasis.

The RCT identified by ChiCTR2100047962 was conducted by Zhao Rong et al[96] to investigate the impact of the Chaihuaji Recipe on peripheral blood inflammatory cytokines and basic fibroblast growth factor (bFGF) in patients with TACE syndrome associated with HCC. This study focused on key biomarkers, including bFGF, matrix metalloproteinase-9 (MMP-9), and vascular endothelial growth factor (VEGF). A total of 105 patients with HCC who experienced postoperative TACE syndrome were recruited and randomly assigned to either a control group or an observation group. The control group consisted of 53 patients who received standard Western medical treatment, while the observation group, comprising 52 patients, was administered the Chaihuaji Recipe orally, at a dosage of one dose per day, in the morning and evening, in addition to the standard treatment. Both groups underwent treatment for a duration of seven days. Additionally, a cohort of 20 healthy volunteers was included as the healthy control group. Serum levels of C-reactive protein (CRP), interleukin-12 (IL-12), bFGF, MMP-9, and VEGF were measured and compared among the healthy, control, and observation groups using an enzyme-linked immunosorbent assay (ELISA). The study also evaluated the TCM syndrome scores and clinical efficacy between the observation and control groups, before and after treatment. Furthermore, comparisons were made regarding the levels of bFGF, IL-12, MMP-9, and VEGF within the observation group pre- and post-treatment, as well as among the operation group post-treatment, at the same PHC stage. The safety profiles of the control and observation groups were assessed throughout the treatment period. The findings of this study indicate that the Chaihuaji Recipe has the potential to enhance clinical outcomes in HCC patients with TACE syndrome while concurrently reducing the levels of bFGF, IL-12, MMP-9, and VEGF in the peripheral blood.

Shaoyao et al[97] conducted a randomized controlled trial (ChiCTR-TRC-11001384) to investigate the impact of the external application of Jiawei Shuangbai Powder in conjunction with auricular point pressing on pain levels and quality of life in patients with HCC undergoing interventional therapy. This study included 70 patients with HCC who were assigned to two groups. The control group received standard treatment, whereas the experimental group received external application of modified Shuangbai Powder along with auricular point pressing. The researchers compared the therapeutic outcomes, pain scores, TCM symptom scores, factors contributing to pain, and quality of life scores before and seven days post-intervention between the two groups. The findings indicated that the external application of Jiawei Shuangbai Powder combined with auricular point pressing significantly alleviated pain in patients undergoing interventional therapy for HCC, enhanced symptom relief, improved hemorheological parameters, and positively influenced patients' quality of life.

The mechanism diagram of TCM in treating HCC is summarized as follows, as shown in Figure 1.

The methods of TCM treatment for HCC are summarized in Table 1.

Discussion

Advancements in contemporary technology, coupled with the rapid evolution of TCM, have led to a growing global acknowledgment of the therapeutic efficacy of various TCM modalities. TCM has garnered significant attention from the medical community because of its pronounced clinical effectiveness in cancer treatment, particularly in extending patient survival and enhancing quality of life; however, the precise mechanisms underlying its action warrant further investigation.[98] TCM's holistic approach systematically regulates the body, demonstrating its capacity to inhibit tumor growth through multiple targets, pathways, and levels, which constitutes a distinct advantage in disease management. Nevertheless, the intricate chemical composition of TCM compounds presents a significant challenge in elucidating their anti-tumor mechanisms.

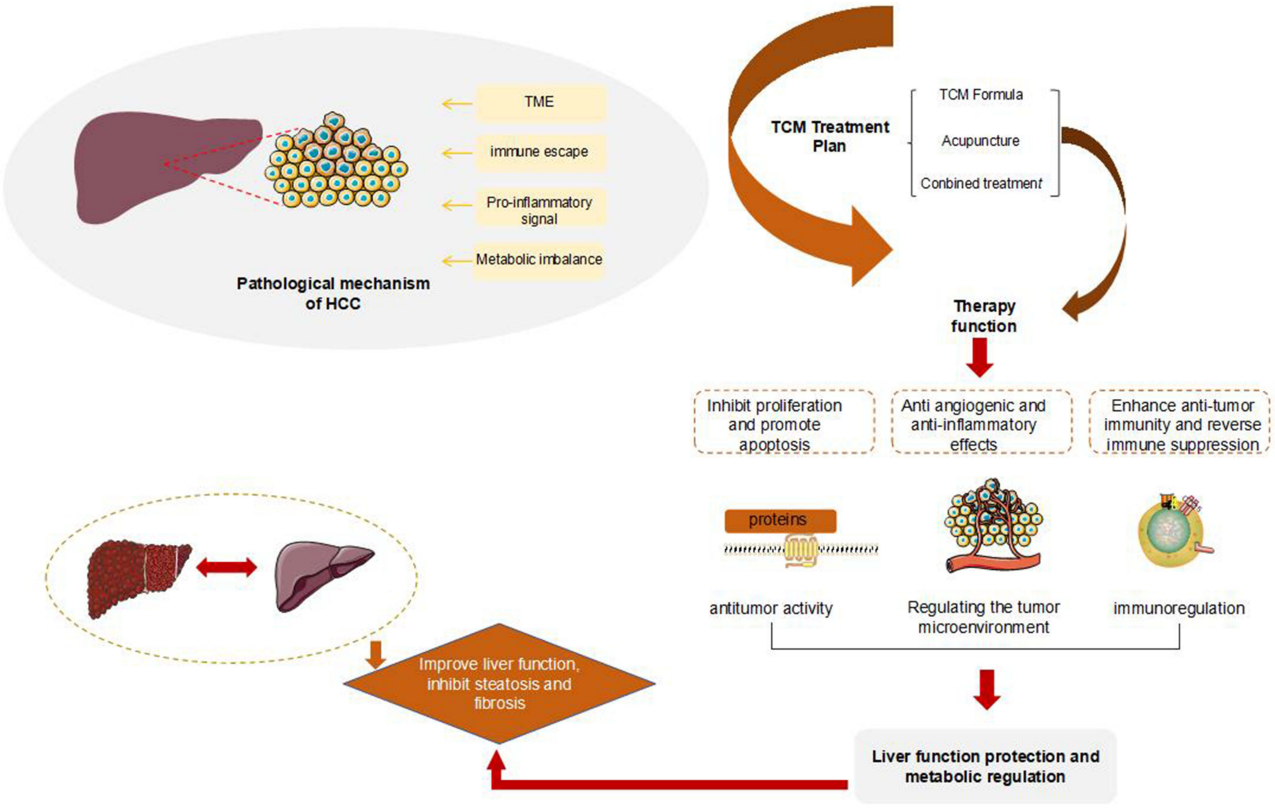

Figure 1 The mechanism of TCM in the treatment of HCC.

Currently, there is growing interest in investigating the molecular and genetic mechanisms by which TCM exerts its anti-liver cancer effects. The complexity and diversity inherent in TCM's mechanisms of action of TCM necessitates unique research methodologies. If researchers focus solely on the differential expression of a limited number of proteins within one or a few signaling pathways while neglecting the interconnectedness of complete pathways or complex signaling networks, a comprehensive understanding of the mechanisms of TCM compounds in liver cancer treatment may remain elusive. Employing large-scale network data, along with gene, proteomic, and metabolomic analyses within a systems biology framework, could facilitate a more systematic exploration of the upstream and downstream regulatory genes and target proteins involved in the multi-signal transduction systems of TCM's anti-liver cancer effects of TCM. Furthermore, utilizing docking technology in network pharmacology to correlate the active components of TCM with their anti-liver cancer properties could yield a more thorough understanding of TCM's mechanisms of TCM.

Building on this foundation, experimental investigation of TCM compound prescriptions, acupuncture, moxibustion, and other therapeutic modalities can be effectively integrated into clinical practice, thereby showcasing the clinical efficacy of TCM and enhancing its global recognition.

Table 1 Treatment of HCC With TCM

Treatment	Mechanism of Action
Huqi Zhengxiao Prescription	Oral administration of Huqizhengxiao Formula can improve the survival rate, prolong the survival time and improve the quality of life of stage III HBV-related HCC patients with syndrome of deficiency of vital qi and accumulation of toxin and blood stasis.
Bupleurum huaji prescription	Chaihu Huaji Recipe can improve the clinical signs of HCC patients with post-Tace syndrome, and reduce the levels of bFGF, IL-12, MMP-9 and VEGF in peripheral blood.
External application of modified Shuangbai powder combined with ear acupoint pressing bean	It can effectively relieve the pain degree of patients with HCC interventional therapy, improve symptoms and hemorheology, and improve the quality of life of patients.

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A systematic approach to HCC pathogenesis emphasizes the development of more precise and effective treatment strategies through a comprehensive understanding of the mechanisms underlying HCC morbidity. This strategy encompasses an in-depth examination of HCC's onset and progression of HCC, including gene mutations, alterations in signaling pathways, and the influence of the tumor microenvironment. Such investigations may reveal commonalities in the development of HCC, thereby offering novel insights into therapeutic interventions.

Plant extracts represent a significant component of therapeutic strategies based on systemic mechanisms of morbidity.[99] Numerous phytochemicals have demonstrated antitumor activity and effectively inhibit HCC growth and metastasis. For instance, certain plant extracts have been shown to impede tumor cell proliferation, induce apoptosis, and obstruct angiogenesis, thereby exerting therapeutic effects in HCC. Experimental studies have indicated that specific plant extracts yield substantial therapeutic benefits for HCC; for example, Echinacea purpurea inhibits HCC cell proliferation and promotes apoptosis,[100] whereas green tea extract has been found to prevent HCC growth by inhibiting tumor angiogenesis.[101]

Although large-scale clinical trials validating the efficacy of plant extracts for HCC treatment are lacking, preliminary small-scale clinical trials have yielded promising results. For instance, a small clinical trial involving Echinacea purpurea demonstrated significant symptom improvement in patients with HCC without notable side effects.[100]

Although the application of plant extracts in HCC treatment remains in its nascent stages, existing studies underscore their considerable therapeutic potential. As further plant extracts are discovered and the mechanisms of HCC morbidity elucidated, the incorporation of plant extracts into HCC treatment regimens is anticipated to emerge as a significant avenue for future research. This development may provide additional therapeutic options for patients with HCC, potentially enhancing treatment outcomes and improving their quality of life.

Abbreviations

HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; SVR, sustained virological response; TCM, Traditional Chinese Medicine; SEER, Surveillance, Epidemiology, and End Results; NASH, non-alcoholic steatohepatitis; ASH, alcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver disease; TCGA, The Cancer Genome Atlas; ICIs, immune checkpoint inhibitors; T_{reg}, regulatory T cells; ER, endoplasmic reticulum; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; TNF, tumor necrosis factor; ROS, reactive oxygen species; GPIbα, glycoprotein Ibα; IL-6, interleukin-6; FASN, fatty acid synthase; PPARγ, peroxisome proliferator-activated receptor gamma; TRF, timed restriction diet; LXR, liver X receptors; CDCA, chenodeoxycholic acid; DNL, de novo lipogenesis; BMI, body mass index; LPS, lipopolysaccharides; GLPS, Ganoderma lucidum; APS, Astragalus polysaccharide; KPS, Karnofsky Performance Status; P-gp, P-glycoprotein; MRP2, multidrug resistance-associated protein 2; 5-FU, 5-fluorouracil; ABCG2, ATP-binding cassette sub-family G member 2; RCT, randomized controlled trial; bFGF, basic fibroblast growth factor; MMP-9, matrix metalloproteinase-9; VEGF, vascular endothelial growth factor; CP, C-reactive protein; IL-12, interleukin-12; ELISA, enzyme-linked immunosorbent assay.

Disclosure

The authors declare that they have no affiliation with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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