

An Overview of Traditional Chinese Medicine in the Treatment After Radical Resection of Hepatocellular Carcinoma

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Abstract: According to the Barcelona Clinic Liver Cancer (BCLC) system, radical resection of early stage primary hepatocellular carcinoma (HCC) mainly includes liver transplantation, surgical resection, and radiofrequency ablation (RFA), which yield 5-year survival rates of about 70–79%, 41.3–69.5%, and 40–70%, respectively. The tumor-free 5-year rate for HCC patients undergoing radical resection only reach up to 13.7 months, so the prevention of recurrence after radical resection of HCC is very important for the prognosis of patients. The traditional Chinese medicine (TCM) takes the approach of multitarget and overall-regulation to treat tumors, it can also independently present the “component-target-pathway” related to a particular disease, and its systematic and holistic characteristics can provide a personalized therapy based on symptoms of the patient by treating the patient as a whole. TCM as postoperative adjuvant therapy after radical resection of HCC in Barcelona Clinic liver cancer A or B stages, and the numerous clinical trials confirmed that the efficacy of TCM in the field of HCC has a significant effect, not only improving the prognosis and quality of life but also enhancing patient survival rate. However, with the characteristics of multi-target, multi-component, and multi-pathway, the specific mechanism of Chinese medicine in the treatment of diseases is still unclear. Because of the positive pharmacological activities of TCM in combating anti-tumors, the mechanism studies of TCM have demonstrated beneficial effects on the regulation of immune function, chronic inflammation, the proliferation and metastasis of liver cancer cells, autophagy, and cell signaling pathways related to liver cancer. Therefore, this article reviews the mechanism of traditional Chinese medicine in reducing the recurrence rate of HCC after radical resection.

Keywords: traditional Chinese medicine, radical resection, hepatocellular carcinoma, recurrence

According to estimates from the global cancer statistics by the International Agency for Research on Cancer, there were 905,677 new cases and 830,180 liver cancer deaths worldwide in 2020. Primary liver cancer is expected to rank as the sixth most commonly diagnosed cancer and the third leading cause of cancer death worldwide in 2020.^{1,2} Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer, as the safety of surgical techniques for hepatectomy improves, as well as the advancement of systemic treatments and the greater availability of local treatments, early-stage HCC patients are more eligible to receive curative therapies, such as surgery and ablation, that significantly improve overall survival (OS).^{3,4} At present, the strategies of radical resection of HCC are diversified, including liver resection, liver transplantation, and ablation surgery. However, the overall prognosis for HCC is poor, with a 5-year recurrence rate around 70% either to local recurrence or distant metastasis.⁵ There is a multicenter study of 734 patients, among 303 patients who developed late HCC recurrence 2 years, the recurrence was associated with sex, cirrhosis, and several aggressive tumor characteristics of the initial HCC.^{6,7} Liver transplantation is the most effective method for the treatment of HCC. However, due to the limited liver source, it cannot satisfy most patients. Therefore, the current controversial

issues mainly focus on the effectiveness and recurrence between hepatectomy and ablation.⁸ The surgical resection (SR) in treating small hepatocellular carcinoma (SHCC) has higher long-term survival rate and a lower long-term recurrence rate, and radiofrequency ablation (RFA) led to a lower complication rate than SR.⁹ With long-term use, chemotherapeutic drugs, such as sorafenib, have additional issues such as toxicity and/or drug inefficacy. As a result, both current ablation therapies or hepatectomy are inevitable for the recurrence, and further research to find better methods for preventing recurrence of HCC is necessary.

As a complementary and alternative medicine treatment, Traditional Chinese Medicine (TCM), especially herbal medicine, has an extensive history and been widely used in cancer treatment in China.^{10,11} Pharmacological research has shown that TCM has been used as a two-way immune regulator with anti-inflammatory,¹² immunoregulatory,¹³ and anti-angiogenic effects.¹⁴ A large number of clinical trials confirmed that the efficacy of TCM in the field of HCC, not only improving the prognosis and quality of life but also enhancing patient survival rate.¹⁵ The results of several randomized controlled studies have shown that the oral Chinese medicine combined with targeted therapy and immunotherapy can significantly enhance the therapeutic efficacy and reduce the adverse reactions caused by targeted therapy in patients with HCC.^{16,17} The poor prognosis for radical resection of HCC has led scientists and physicians to search for novel treatment options to improve patient survival. TCM gives new horizons for improving the outcomes of malignancies. In this paper, we describe the mechanism of TCM in the treatment and prevention of recurrence after radical resection of HCC.

Risk Factors for Early Recurrence After Radical Resection of HCC

Hepatectomy represents the first-line treatment for patients with resectable hepatocellular carcinoma (HCC).¹⁸ However, it has been reported that the 5-year recurrence rate of HCC is as high as 50% and 70%.¹⁹ The main risk factors for recurrence in early-stage HCC patients after radical resection are ascites, higher Child-Pugh score, larger tumor size, low platelet count, liver cirrhosis, elevated α -fetoprotein (AFP) level, and high serum hepatitis B virus (HBV) load.^{20–22} The factors for recurrence after radical resection of HCC could be divided into three categories: tumor, host, and surgical factors. a) tumor factor: microscopic venous invasion as well as macroscopic portal vein involvement are both major risk factors as metastasis via portal venous system.²³ Large tumors, especially tumors larger than 5 cm, significantly increase the risk of postoperative recurrence.²⁴ The larger diameter of the tumor, the greater the possibility of vascular invasion and distant metastasis, which increases the risk of surgery, causing liver metastasis and recurrence and affecting the survival of patients. In addition, the nuclear DNA content in tumor cells has been shown to be closely related to the malignant potential of the neoplasm, and DNA aneuploidy was thought to have prognostic significance in many kinds of malignant tumors.²⁵ Proliferating cell nuclear antigen (PCNA) is an accessory protein of DNA polymerase delta, its expression is related to DNA synthesis and cell replication, the sign of the G1/S phase of the cell cycle, and can be evaluated by immunohistochemical studies.²⁶ (b) Surgical factors: the type of resection (anatomic vs non-anatomic), the extent of resection margin and perioperative blood transfusion are the three most extensive surgical factors impacting postoperative recurrence. But also some studies shown that the type of resection (anatomic vs non-anatomic) is not considered a distinct risk factor for early (2 year) tumor recurrence in patients with HCC and preserved liver function.²⁷ Few studies have argued that intraoperative blood loss and perioperative transfusion not only increase the risk of operative morbidity and mortality but also jeopardize long-term survival, since they actually increase the recurrence rate of the tumor being resected.^{28,29} Intraoperative procedures for liver cancer, especially large tumors, have been considered to be an important factor leading to the spread of tumor cells in the portal system, which can explain the cause of early recurrence in the liver after resection. (c) Host factors: However, age and gender have also been reported as independent risk factors. The difference in prognosis between men and women among HCC patients may be mainly attributed to estradiol.³⁰

Adjuvant Treatment for Prevention of Recurrence After Radical Operation of HCC

Radical excision is the main surgical treatment for HCC, but the high metastasis and relapse rates after operation severely affect the long-term survival of patients. There are many adjuvant treatment methods to prevent HCC recurrence after radical surgery, such as antiviral therapy, which has potential advantage in terms of reducing the recurrence rate and improving the overall survival (OS) and/or disease-free survival of patients with hepatitis-related HCC.³¹ In addition,

studies believe that preoperative transcatheter arterial chemoembolization (TACE) can also significantly reduce the intrahepatic recurrence rate and improve OS, especially for patients with a higher risk of recurrence.³² Increasing evidence reveals that TACE after radical resection of primary HCC is beneficial for the treatment outcome.³³ A randomized controlled trial (RCT) showed that postoperative adjuvant TACE (PATAACE) conferred more benefits for HCC patients with high risk of recurrence, such as large tumor diameter (>5 cm), macroscopic vascular invasion, and multiple tumor nodules.³⁴ The efficacy of molecular targeted drugs has brought new hope for patients. Early adjuvant adoptive immunotherapy can significantly improve clinical prognosis. In recent years, sorafenib, lenvatinib, Regorafenib, and Cabozantinib are being explored for prevention of recurrence after radical operation of HCC. Lenvatinib has been approved by the FDA as a first-line treatment for patients with unresectable HCC. Regorafenib has been approved by the FDA as a second-line treatment for patients with advanced HCC who have failed sorafenib. Cabozantinib has been approved by the FDA as a second and third line agent for advanced HCC. Adjuvant lenvatinib therapy after radical resection in patients with China liver cancer staging (CNLC) IIb and/or IIIa HCC resulted in a 1-year recurrence-free survival rate of 50.5% and a median RFS of 16.5 months. In a prospective study of lenvatinib combined with TACE followed by adjuvant therapy for HCC with high-risk recurrence factors, the disease-free survival (DFS) was 17 months, while the median DFS of TACE in the control group was 9 months.³⁵ Numerous clinical trials are now underway to evaluate the efficacy of immune checkpoint inhibitors for patients with many kinds of cancer, including HCC, and the outcomes of these trials are highly anticipated. In addition, the application of Chinese medicine provides new insights for the treatment of HCC after radical resection. Huaier Granule is a kind of traditional Chinese medicine, which has the function of prolonging the recurrence-free survival period and reducing extrahepatic recurrence.³⁶ A multicenter, randomized, clinical trial involving 39 centers and 1044 patients nationwide demonstrated that the traditional Chinese medicine Huaier Granules as a postoperative adjuvant treatment after radical hepatectomy of HCC in Barcelona Clinic Liver cancer A or B stages had significant RFS prolongation and reduced extrahepatic recurrence.^{37,38} The TCM plays an important role in reducing the recurrence and metastasis of HCC after radical resection, prolonging the survival time, and improving the quality of patients' life. The current application of TCM mainly includes Chinese medicine prescriptions and Chinese patent medicine, shown in Table 1 and Table 2. With its unique development concept and its own theoretical system, Chinese medicine has a certain degree of existence in modern research. TCM has the synergistic regulation of multi-components, multiple targets, and multiple pathways, and it is necessary to understand an effective drug derived from TCM or active components for HCC treatment and to discuss their mechanisms of treatment.

The Mechanism of TCM in Preventing and Treating HCC

Suppression of Proliferation and Cell Cycle Arrest

The critical component of tumor occurrence is tumorigenesis, resulting in loss of programmed cell death through genetic changes.⁵⁹ Cell cycle regulators are the products of genes that appear to control apoptotic.⁶⁰ There are two apoptotic pathways: a) mitochondrial-dependent intrinsic pathway, and b) death receptor-mediated extrinsic pathway.⁹⁹ Furthermore, the tumor suppressor P53 activate various cellular reactions, and the abnormal regulation of p53 leads to cell cycle arrested and apoptosis.⁶¹ The uncontrolled progression and proliferation of cell cycle in cancer cells has been known to be a major indicator for tumor development and proliferation, cell cycle arrest has been implicated anticancer effects.¹⁰⁰ Studies found that Tetramethylpyrazine (isolated from *Ligusticum chuanxiong*) induced a significant cell-cycle arrest in the G0/G1 phase during cell cycle progression and apoptosis.⁷⁸ Studies have also mentioned that TCM can affect tumour progression by influencing cell cycles, including HCC, cervical cancer, nasopharyngeal carcinoma and breast cancer.⁷⁹ TCM plays a more important role in the G1/S checkpoint pathway and proteins related to the G1/S phase, cyclinD1 is a cell cycle-related protein in G1/S phase, promoting cell from G1 phase into S phase and commence the DNA replication.¹⁰¹ Some researchers have proved that the proliferation of tumor cells and the inhibition of tumor growth may also be caused by apoptosis and G2/M phase arrest. TCM inhibited tumor growth by inducing G2/M cell cycle block, which has a different mechanism of action from Sorafenib.¹⁰² Its main targets are serine-threonine kinase Raf-1, vascular endothelial growth factor receptor and platelet-derived growth factor sorafenib, which seem to be effective in prolonging the median survival of patients with liver cancer, but its response rate is very low and may cause drug resistance in some patients.⁶² Interestingly, the research results show that

Table I Traditional Chinese Prescriptions for HCC Treatment and Prevention of Recurrence

Prescription	Active Ingredients Identified by HPLC-MS/MS	Effect	Signaling Pathway	References
Fuzheng Jiedu Xiaoji formulation	Ormononetin, chlorogenic acid (CGA), caffeic acid, luteolin, gallic acid, diosgenin, ergosterol endoperoxide, and lupeol	Inhibits hepatocellular carcinoma progression	AKT/CyclinD1/p21/p27	Yang X. et al ³⁹
Compound kushen injection	Matrine	Regulate macrophages in the immune microenvironment	TNFR1/NF-κB and MAPK axis	Yang et al ⁴⁰
Huanglian Jiedu Decoction	Geniposide, berberine and baicalin et al	Suppressed growth and angiogenesis	AMPK signaling	Wang N et al ⁴¹
Gehua Jiecheng Decoction	New hesperidin; Puerarin; Genistein glycoside; Puerarin-4'-O-glucoside et al	Antagonized the immunosuppressive; anti-inflammatory and antiangiogenesis effects	WNT1, β-catenin, NF-κB, p-MAPK, p-AKT, and p-SRC	Cheng C et al ⁴²
Qizhu decoction	P. cuspidatum and P. urinaria, such as corilagin, polydatin, resveratrol, quercetin, emodin, and rutin	Inhibit hepatitis and hepatocellular carcinoma	Suppressing NF-κB signaling	Wan LF et al ⁴³
Zuo-Jin-Wan	Berberine and evodiamine	Orthotopic HepG2 xenograft immunocompetent mice	c-myc	Chou ST et al ⁴⁴
Jiedu Recipe	–	Inhibits the Epithelial Mesenchymal Transition of Hepatocellular Carcinoma	Smad2/3Pathways	Liang S et al ⁴⁵
Huqizhengxiao (HQZX) Decoction	–	Inhibition of Telomerase Activity in Nude Mice of Hepatocarcinoma Xenograft	STAT3 and ERK signal pathway.	Yu X et al ⁴⁶
Yin Yang Gong Ji pill (YYGJ)	Cinnamaldehyde, 6-gingerol, evodiamine, aconitine, isorhamnetin, and syringaldehyde	Inhibited HepG2 and MHCC97H cell proliferation	MMP2 and E-cadherin	Li, Yongwei et al ⁴⁷
Bear Bile Powder	–	Inhibits Growth of Hepatocellular Carcinoma	STAT3 Signaling Pathway	Chen HW et al ⁴⁸
<i>Phyllanthus urinaria</i> L. (CP)	Gallic Acid, Calycosin-7-glucoside and Luteolin	Suppressing metastasis of HBV-associated HCC	Akt/GSK3β/β-catenin axis	Huang D et al ²²
Pien Tze Huang (PZH)	Ginsenosides Re, RgI, RbI, Rd, and muscone	Anti-inflammation and induction of G2/M arrest	NF-κB, TNFR1, TNFR2, P53, and IL-6 pathways	Fan D et al ⁴⁹
Aidi injection	Viz. cantharidin, syringin, calycosin-7-o-β-Dglucoside, isozinpidine, ginsenosides Rd, Rc, RbI, Re, and RgI, astragalosides II and IV, and eleutheroside E.	Inhibited the proliferation of HepG2	PI3K/Akt and MAPK signal transduction pathways	Lan HY et al ⁵⁰
Huxie Huaji (HXHJ) Ointment	Succinic acid, Caffeic acid, 3-Caffeoylquinic acid, et al	Cell mitochondrial apoptosis	p53/Bcl-2/Cyt-C/caspase-3 signaling pathway	Cai Y et al ⁵¹

(Continued)

Table 1 (Continued).

Prescription	Active Ingredients Identified by HPLC-MS/MS	Effect	Signaling Pathway	References
Shufeng Jiedu Capsule (SFJDC)	Resveratrol, quercetin, et al	Antiviral, antibacterial, antitumor, and anti-inflammatory	Akt/mTOR, and NF- κ B signaling pathways.	Xia J et al ⁵²
Huanglian decoction	Berberine hydrochloride	Inhibit HCC cell growth	p53 signaling pathway	Li M et al ⁵³
Fuzheng Xiaozheng prescription (FZXZP)	445 compounds	Anti-inflammation and promoting the lipid related metabolisms	PPAR signaling pathway	Li X et al ⁵⁴
Gansui-Banxia Decoction (GSBXD)	–	Exhibited antitumor immune activity	AKT/STAT3/ERK signaling pathway	Feng XY et al ⁵⁵
Fuzheng Qingjie Granules	Vanillic acid, Mairin, alexandrin, et al	Egulating immune function and inducing mitochondria mediated apoptosis.	Caspase	Chen X et al ⁵⁶
Yanggan Huayu granule	Stigmasterol, campesterol, demethoxycurcumin, et al	Apoptosis	AKT	Shen Y et al ⁵⁷
Yanggan Jiedu Sanjie (YGJDSJ) formula	β -elemene	Inhibited cell proliferation	CDKN1a/CDKN2a-RB signalling	Hu B et al ⁵⁸
Dahuang Zhechong Pill	–	Regulating Energy Metabolism	PARP	Wu L et al ⁵⁹

Table 2 Traditional Chinese Herbs and Their Active Ingredients for HCC Treatment and Prevention of Recurrence

Active ingredients of Chinese Medicine	Source of Chinese Medicine	Signaling Pathway	Effect	References
Ginsenoside Rg3, Actinidia Chinensis Planch Root extract, Cordycepin, Rheum palmatum extract, Cinobufacini, Euphorbia factor L2	Panax Ginseng C. A. Mey., Zanthoxylum avicennae (Ying Bu Bo, YBB), Actinidia Chinensis Planch Root, Cordyceps, Radix Rhei Et Rhizome, Bufo bufo gargarizans Cantor, Huaier, Euphorbia pekinensis Rupr.	ARHGAP9, GSK-3 β , DLX2/TARBP2/JNK/AKT, NF- κ B p, JAK2/STAT3, c-Met/ERK, Decreased Yes-Associated Protein 1, AKT/STAT3signaling pathway	Inhibited the migration and invasion of tumor cells	Sun MY et al, Wu HC et al, Tan ZB et al ^{16,60,61}
Norcantharidin (NCTD) and Coix lacryma-jobi seed oil (CLSO), Dendrobium candidum extract (DCE), Ginkgo biloba extract EGb761	Coicis Semen and Mylabris, Dendrobium candidum, Ginkgo Folium	FoxP 3, Wnt/ β -catenin, NF- κ B/p53	Apoptosis and inhibits tumor cell proliferation	Wang D et al, Guo Z et al, Wang R et al ^{62–64}
Dulcitol, magnolol, Gigantol, Prunella vulgaris total flavonoids	Euonymus alatus, Cistanche tubulosa (Schenk) R., Magnolia Officinalis Rehd Et Wils, Dendrobium nobile Lindl, Prunella vulgaris	MMPs, SIRT1/p53, caspase-7, ERK/NF- κ B, PI3K/Akt/NF- κ B, PI3K/Akt/mTOR pathways.	Inhibited tumor cells proliferation	Lin XL et al, Yuan P et al, Tsai JJ et al, Song YG et al ^{65–68}

(Continued)

Table 2 (Continued).

Active ingredients of Chinese Medicine	Source of Chinese Medicine	Signaling Pathway	Effect	References
Sennoside A (SA), Salidroside (SDS), Matrine	<i>Rheum officinale</i> Baill., <i>Rhodiola rosea</i> L., <i>Radix Sophora flavescens</i>	Wnt, TNF, VEGF and NF- κ B, Notch1, MMP9, signaling pathway	Inhibit HCC metastasis	Le J et al, Lu L et al, Zhang J et al ⁶⁹⁻⁷¹
Echinacoside (ECH), arctigenin, Tanshinone IIA (TanIIA); Cryptotanshinone (CPT) and dihydrotanshinone (DHT), Curcumenol and laminarin, Chinese dragon's blood EtOAc extract (CDBEE)	Cistanches Herba, Burdock (<i>Arctium lappa</i>), <i>Salvia miltiorrhiza</i> , <i>Curcumae longae</i> Rhizoma and kelp, <i>Dracaena cochinchinensis</i> (Lour.) S. C. Chen	PI3K/AKT, PPAR- α , TGF- β ; EGFR, TGF- β /Smad3 signaling	Against liver cancer growth	Ye Y et al, Sun Y et al, Ma L et al ^{72,73,120}
Quercetin	<i>Artemisiae Scopariae Herba</i>	BIRC 5	Immunotherapy	Mo Z et al, ⁷⁵
Luteolin, Aconitine, total Flavonoids from <i>Oroxylum indicum</i> , Flavonoids, Psoralidin	<i>Lonicerae Japonicae Flos</i> , <i>Perilla Frutescens</i> , <i>Aconiti Lateralis Radix Praeparata</i> , seeds of <i>Oroxylum indicum</i> (L.) Vent., <i>Dendrobium denneum</i> paxt., <i>Psoralea corylifolia</i> Linn.	bcl-2, PI3K/Akt/PTEN Signaling Pathway; Caspase-3/P53	Apoptosis	Qi X et al, Li NN et al ^{76,77}
Tetramethylpyrazine, Digitoxin, Total alkaloids of <i>Rubus alceifolius</i> Poir; Arabinogalactan, Aloperine	<i>Ligusticum chuanxiong</i> hort, Saffron, <i>Digitalis</i> , <i>Rubus alceifolius</i> Poir, <i>Lycii Fructus</i> , <i>Sophora alopecuroides</i> L.	p53, Bax, caspase-3, MAPK, Notch and STAT3 Signaling Pathway	Cell cycle arrest and apoptosis	Bi L et al, Liu T et al, Lei Y et al ⁷⁸⁻⁸⁰
Alkaloids of <i>Coptidis rhizome</i> ; Berberine	<i>Coptidis rhizome</i>	Increased the phosphorylation of eukaryotic elongation factor 2 (eEF2); NF- κ B	Suppression of vascular endothelial growth; apoptosis	Tan HY et al, Li M et al ^{53,81}
Andrographolide	<i>Andrographis Herba</i>	VEGFA	Inhibit Vascular endothelial growth	Shi L et al ⁸²
Astragali Polysaccharide and Curcumin	<i>Huangqin Scutellariae Radix</i> and <i>Curcumae longae Rhizoma</i>	CD31 and NG2	Tumor Vascular Normalization	Tang D et al ⁸³
Curcumin	<i>Curcumae longae Rhizoma</i>	ERK1/2, p38 MAPK and JNK signaling pathways and TLR4/NF- κ B signaling pathway; glypican-3/Wnt/ β -catenin signaling pathway	Suppressed EMT and blocked G2/M phase progression; autophagy	Qu J et al, Tian S et al, Hu P et al ⁸⁴⁻⁸⁶
Dioscin	<i>Rhizoma Dioscoreae</i>	TP53, BAX, BCL2 and CASP3	Apoptosis and increased DNA damage	Zhang G et al ⁸⁷
HI, a derivative of tetrandrine	<i>Stephaniae Tetrandrae Radix</i>	STAT3/MCL-1 and PUMA	Enhances the efficacy of 5-FU in Bel7402/5-FU cells	Li F et al ⁸⁸
<i>Ganoderma lucidum</i> polysaccharide	<i>Ganoderma</i>	Akt signaling pathway	Enhances radiosensitivity of hepatocellular carcinoma cell	Yu Y et al ⁸⁹

(Continued)

Table 2 (Continued).

Active ingredients of Chinese Medicine	Source of Chinese Medicine	Signaling Pathway	Effect	References
Saikosaponin-d	Radix Bupleuri	LC3-II; SUMO1 and GLI proteins	Autophagy; Enhances Chemosensitivity	Tian YD et al, Zhang CY et al ^{90,91}
Cytisine	Small tree Sophora Alopecuroides L.	CHOP and p-JNK1/2	Endoplasmic reticulum stress	Yu L et al ⁹²
1 β -hydroxyl-arenobufagin (1 β -OH-ABF); Bufalin	Chansu	mTOR signaling; β -catenin/TCF signaling	Mitochondrial apoptosis	Deng LJ et al, Yu Z et al ^{93,94}
Scutellarin	Erigeron breviscapus (Vant.) Hand. -Mazz.	JAK/STAT signalling pathway	Inhibition of the EMT process	Liu K et al ⁹⁵
Ginsenoside Rg1	Panax Ginseng C. A. Mey.	Nrf2 signaling pathway	Antioxidant activities	Gao Y et al ⁹⁶
Celastrus orbiculatus Thunb. extracts (COE)	Celastrus orbiculatus Thunb.	mTOR signal pathway.	Antineoplastic	Qian YY et al ⁹⁷
Platycodin D	Platycodon grandiflorus (PG)	ERK1/2-mediated cofilin-1 phosphorylation	Reverses histone deacetylase inhibitor resistance	Hsu WC et al ⁹⁸

TCM has a stronger effect on PI3K and PTEN signaling pathways, and induces G2/M phase block in the cell cycle.^{77,103} In addition, Chinese medicine has advantages in anti-inflammatory and can make up for the shortcomings of Sorafenib.⁶³ The role of traditional Chinese medicine suggests that its combined application with Sorafenib can not only improve the curative effect of liver cancer after radical resection but also reduce the drug resistance to Sorafenib and the rate of tumor recurrence.^{60,64}

Anti-Inflammatory

Most importantly, the Inflammation-mediated liver injury after radical resection of HCC is the key cause of recurrence and distant metastasis.^{54,90,91} A study has found that the levels of inflammatory factors such as TNF- α , IL-6 and IL-8 in cancer patients before radiotherapy were significantly higher than those in the control group, suggesting that the patients were in an inflammatory response activation state.¹⁰⁴ At the cellular and molecular levels, the anti-carcinogenic effects of TCM have been associated with the modulation of multiple inflammatory signal transduction pathways, including Janus kinase (JNK)/signal transducer and activator of transcription 3 (STAT 3) signaling pathways,¹⁰⁵ phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin (PI3K/AKT/mTOR)⁶⁹ and MAPK, AMPK,⁷⁰ EGFR,⁷² nuclear factor kappaB (NF- κ B) signaling pathway,⁷³ can regulate a variety of inflammatory factors, including TNF- α and IL-6.^{106,107} The MAPK/p38 signaling pathway not only regulates the expression of pro-inflammatory cytokines but also plays an important role in the activation of cell adhesion, migration, and invasion in HCC patients. The STAT 3 signaling pathway is a pro-inflammatory pathway, which may be triggered by tumor cells. As a tumor suppressor, FOXO negatively regulates the expression of immunosuppressive proteins to promote tumor anti-tumor activity.¹⁰⁸ The studies found that Extracts of Qizhu decoction⁴³ and Benzophenones from *Anemarrhena asphodeloides* Bge¹⁰⁹ exhibit anticancer activity via the traditional inflammatory NF- κ B signaling pathway.

Traditional Chinese medicine plays an important role in targeting the body's inflammatory response and immunity, multiple types of cells in the liver, including Kupffer cells and other non-parenchymal cells, can be activated by active ingredients of TCM to release chemokines, cytokines that play a major role in regulating the proliferation of T-cells, and

adjusting the proportion of Th1/Th2 cell.¹⁰⁴ The active ingredients of TCM to reduce the inflammation after radical resection and their possible mechanisms of action are as follows: a) regulating immune cell function, inhibiting inflammatory response, improving barrier function and modulating related signal transduction pathways.¹¹⁰ b) regulation of the expression of pro-inflammation genes and cytokines and their receptor on immune cells.⁶⁵ c) promoting anti-inflammation cytokine release, and down-regulate the expression of TLR4/NF-kappaB signaling pathway.^{54,66} d) stimulating the immune-cell mobilization response in the cancer microenvironment, regulating the infiltration of immune NK cells.⁶⁷ e) inhibition of signal transducers and transcription response to inflammatory cytokines. f) depletion of immune and inflammatory cells that promote tumor development and progression.⁷¹

Immunoregulatory

Immunization to treat HCC has a long history.¹¹¹ Dunn et al proposed the tumor immune editing theory for the first time and categorized immune interaction with cancer into three stages: elimination by immunosurveillance mechanisms; equilibrium and escape.¹¹² The theory has extended our understanding of interactions between immune system and tumor cells. First, the immune system surveys for and clears most of the malignant cells; When a small number of malignant cells had evaded the first phase are primed with further editing and enter the “equilibrium” phase, and the equilibrium period can even cover the entire life process of the body in extreme cases; but once the active role of malignant tumor cells breaks this equilibrium state, the tumor cells will successfully “escape” and cause the immune system to lose its effect on the tumor.¹¹³ Tumor cells may cause local or systemic immunodeficiency, such as a significant reduction in the number of CD4+ T cells in cancer patients, dendritic cell dysfunction, and higher levels of immunosuppressive factors (such as transforming growth factor- β).⁵⁶ Immunotherapy is considered a promising cancer treatment method. Chinese medicine emphasizes the importance of enhancing the immune function of cancer patients. Therefore, Chinese medicines for strengthening the body and clearing away heat and detoxification are widely used in the adjuvant treatment of cancer. According to the basic treatment principles of malignant tumors documented in TCM literature, they mainly contained reducing phlegm and resolving masses, promoting blood circulation and detoxification, promoting the body’s resistance, eliminating pathogenic factors, and purging and tonifying in combination, which are widely used in the adjuvant treatment of HCC.¹¹⁴ Herbs for promoting the body’s resistance, such as *Ganoderma lucidum*,⁷⁴ *Astragalus membranaceus*,¹¹⁵ and *Ginseng*,¹¹⁶ are found to promote cytokines (such as interleukin (IL), tumor necrosis factor (TNF), interferon) and alexins, activating T lymphocytes, B lymphocytes, macrophages, natural killer (NK) cells, and dendritic cells. In the tumor microenvironment, the interaction between the host immune system and tumor cells plays an important role in the pathological progression of tumors. Additional studies demonstrated that Ginsenoside Rg3 exhibited immunomodulatory activity by reducing the levels of the cytokines IFN- γ and IL-2, rescuing the levels of CD4+ T cells, enhancing the cytotoxic activities of natural killer (NK),¹⁶ and inhibiting tumor recurrence by regulating the body’s immunity.

Inhibiting Epithelial–Mesenchymal Transition (EMT) of HCC

The TCM has been used for the prevention of recurrence and metastasis of HCC after radical resection for attenuating toxicity and prolonging the survival of HCC patients after surgery.⁵⁷ The occurrence of tumor Epithelial–Mesenchymal Transition (EMT) is closely related to the tumor migration and invasion. EMT is a key biological process in cancer progression and recurrence, the loss of cell–cell interaction and apical-basal polarity, as well as the enhancement of cell motility, drug resistance allows tumor cells to escape from the preinvasive neoplasm, invasion to distant regions and tissues.⁵⁵ E-cadherin is one of the tight junction and adhesion proteins, heavily involved in the responsible for cell adhesion, and polarized distribution of intramembrane proteins, including the Na-K ATPase.¹¹⁷ The lack of E-cadherin leads to the decline of cell adhesion function, thereby detaching the cells and promoting the proliferation, invasion, and metastasis of cancer cells. Furthermore, studies have observed Dulcitol,⁶⁸ a natural product extracted from *euonymus alatus* was reported that it could induce apoptosis of C6 glioma cells and increasing E-cadherin. Furthermore, the Rad-p53 (recombinant human adenovirus p53 is the first commercial product for gene therapy) and curcumin promote HepG 2 cell apoptosis inhibit epithelial–mesenchymal transition (EMT) and block the progression of G2/M cells.^{84,118,119} In addition, TCM inhibits the process of EMT and hinders the metastasis of HCC cells in vivo by down-regulating the expression of transforming growth factor beta receptor 2 (TGF- β 2R) and Smad family member 3 (Smad 3), suggesting

TCM may regulate Smad related pathways to inhibit EMT in HCC.^{39,120} Transforming growth factor β 1 (TGF- β 1) binds to TGF β 1 receptors type I and II (T β RI and T β RII) stimulates the phosphorylation of Smad 2/3 and activation of this Smad-dependent intracellular signaling pathway mediated by Smad-4. Certain studies have noted that the compounds in TCM inhibit tumor growth via regulating TGF- β /Smad signaling pathways. Further mechanistic study Smad pathways control cellular proliferation, differentiation, and apoptosis.^{45,121} Some herbs have the ability to block cellular adhesion and invasion by impacting EMT to mesenchymal-epithelial-transition (MET) phenotypic interconversions.^{122,123} According to previous studies, TGF- β , growth factors including epidermal growth factor (EGF) and hepatocyte growth factor (HGF) trigger downstream signals of EMT through the MAPK and PI3K/Akt pathways.¹²⁴ TCM can inhibit the activation of Akt, ERK, JNK, and p38MAPK, effectively prevent EMT of liver cancer cells, providing a reasonable explanation for its inhibition of liver cancer cell migration and invasion.⁹⁸ Further understanding of the mechanism of action of traditional Chinese medicine in preventing metastasis and recurrence after radical resection of liver cancer provides new ideas.

Induces the Differentiation of Myeloid-Derived Suppressor Cells (MDSCs)

TCM is widely used as an anti-inflammatory, anti-viral and anti-cancer agent and thus can be applied in radical resection of liver cancer. The curcumin, as an active ingredient in turmeric, which acts against a variety of cancers (non-small cell lung cancer, colorectal cancer, liver cancer, and human renal clear cell carcinoma), is anti-inflammatory, choleric, and exerts anti-oxidant effects, without any obvious toxicity in the long term.¹²⁵ Studies suggested that the TCM could increase the number of effector T cells, reduce the infiltration of FOXP3+Tregs, inhibit cytokine-induced apoptosis of effector T cells and expression of tumor immunosuppressive cytokine, mediating M2 TAM transformation to M1 TAM, and change the tumor microenvironment and kill the tumor cells. Some studies have hypothesized that TCM in combination with α -PD-L1 antibody can provide a favorable environment for immune cells response against cancer.^{126,127} Recently, curcumin derivatives were described to inhibit cancer cell proliferation by blocking the activation and expansion of MDSC mediated by STAT3 and NF- κ B signaling pathways.¹²⁸ In-depth research on the pathogenesis of cancer has shown that inflammation and immune microenvironment are the key factors for HCC growth, spread and metastasis after radical resection of HCC.⁴² The tumor microenvironment is filled with regulatory T cells (Tregs), M2 macrophages (TAMs) and myeloid inhibitory cells (MDSCs). MDSCs are significantly found in peripheral blood and solid tumors, maintaining an immune suppressive network in the tumor microenvironment. Previous studies have demonstrated that inhibiting MDSCs in tumors may weaken tumor defense mechanisms and inhibit tumor progression, including lung cancer, malignant melanoma, and liver cancer. The cancer cell-derived GM-CSF is dispensable for the tuning of the tumor microenvironment, with worse prognosis and modulation of inflammation and immunity through recruitment and differentiation of MDSCs. Studies have found that the TCM significantly inhibits the levels of M-CSF, GM-CSF and a variety of inflammatory factors, which provides evidence for the inhibitory effect of TCM on MDSCs and its subsequent anti-liver cancer activity, and TLR4/NF- κ B/Myd88 signaling pathway enhances the immunosuppressive function of MDSC.¹²⁹

Decreasing Telomerase Activity in Precancerous Lesions of Liver

Telomerase is an enzyme, elongates one chain of the telomeric DNA, and compensates for the replication-associated telomere shortening.^{46,130} The telomerase is an attractive therapeutic target, that cancer cells maintain telomeres through activation of the telomerase enzyme and achieve unlimited replication capacity and immortality, complete cancerous transformation.¹³¹ Telomerase has been observed in more than 85% of known human tumors and is considered a promising tumor marker. Researchers have found that TCM such a total alkaloids of mistletoe,¹³² and mistletoe polysaccharides reduce the telomerase activity of liver cancer cells and reduce the telomerase activity of liver precancerous lesions in rats.¹³³ Signal transducer and activator of transcription 3 (STAT3) is an oncogenic transcription factor, is a member of STAT protein family, an important transcription factor of the JAK/STAT signal pathway,^{88,95} belonging to the seven member STAT gene family, playing a key role in many processes such as cell growth and apoptosis. STAT 3 Activate Fos, Cyclin-D, CDC25A, c-Myc or Pim1 and other genes involved in the cell cycle process, up-regulate Bcl-2 (B cell CLL/lymphoma-2), BCLXL, and β 2-macroglobulin to resist apoptosis Gene.^{44,134} Many studies

have found that the TCM reduces the telomerase activity related to significantly reducing P-STAT 3/T-STAT 3, and P-ERK/T-ERK.⁹⁸

Mitochondrial Apoptosis

Liver cancer is a complex interaction among multi-gene, multi-target complex process involving multiple signaling pathways.¹³⁵ There has been a focus on a mechanistic approach for the development of TCM by targeting the induction of apoptotic cell death since apoptosis¹³⁶, or programmed cell death.¹³⁷ Surgical resection of tumors is currently the predominant treatment for HCC, and the multi-kinase inhibitor sorafenib (Nexavar) is an oral drug and a multi-target signal transduction inhibitor, is the first-line drug approved by the Food and Drug Administration (FDA) in 2006 for the treatment of advanced liver cancer.^{40,138} In terms of adverse reactions, HCC patients administered sorafenib mainly included gastrointestinal, physical or skin disease (eg, hand-foot skin reaction, weight loss, hypertension, and diarrhea).¹³⁹ Therefore, it is urgent to explore safely and effectively drugs to induce hepatocyte apoptosis. Chinese herbal medicine and unique biomedical and pharmaceutical resources have been widely used in the prevention and treatment of hepatocellular carcinoma, which can effectively alleviate clinical symptoms, improve immune function, delay the progression of tumors, and improve the quality of life.^{75,140} Modern pharmacology studies have shown that the total saponins obtained from radix *Astragalus membranaceus* could be established as an effective chemotherapeutic agent to suppress cancer cells growth through promoting tumor cells apoptosis and inhibiting tumor angiogenesis and migration.⁵¹ Huanglian Jiedu Decoction and its composition have therapeutic effect on liver cancer, effectively induced hepatocarcinoma cell cycle arrest, and reduced HepG 2 cell anti-apoptosis and expression of protein Bcl-x.⁴¹ TCM can upregulate Bax expression by downregulating Bcl-2 expression in tumor cells, modulating the PI3K/AKT or STAT3 signaling pathway.⁵⁰ Otherwise, TCM inhibited tumor proliferation, migration, and invasion of HCC after HCC surgery through inducing cyclin D1 and cyclin-dependent kinase (CDK1), Bcl-2, MMP-2, MMP-9, and other protein expression, enhance the expression of bax, cleaved Caspase-3, and P21.^{141–143} However, mitochondria still play a central and multifunctional role in the proliferation and growth of malignant tumor cells, which indicates the therapeutic potential in targeting mitochondria.¹⁴⁴ Furthermore, the components of TCM induce apoptosis by up-regulating the expression of tumor suppressor genes p21Cip1/WAF1, p53, the pro-apoptotic protein Bax, activating Caspase apoptotic signals, and down-regulating the expression of the anti-apoptotic proteins Bcl-2, Bcl-XL. P53 is closely associated with cancer inhibition, playing a crucial role in a variety of intracellular and extracellular regulatory mechanisms, activating the target proteins, such as Cdk4, the Cdk inhibitor P21, and cyclinD1, to induce cell cycle arrest and apoptosis.^{145,146} Bcl-2 is the most important anti-apoptotic members in the Bcl-2 family, binding to the pro-apoptotic proteins Bax (Bcl-2-associated X protein) to protect cells against apoptosis by maintaining the integrity of the mitochondrial membrane.¹⁴⁷ Bax is thought to homo-oligomerize and form pores in the outer mitochondrial membrane, leading to the increase of mitochondrial outer-membrane permeabilization (MOMP) and release of apoptogenic mitochondrial intermembrane proteins, such as cytochrome c, binding to the adaptor protein APAF-1 and causing the aggregation and activation of the initiator caspase-9.^{148,149} The anti-apoptotic protein bcl-2 hinders the flow of Ca²⁺ from the endoplasmic reticulum to the cytoplasm, and combines it with bax to form a bax-bcl-2 heterodimer, thereby preventing the occurrence of cell apoptosis.⁷⁶ On the one hand, the ratio of bax/bcl-2 is unbalanced, forming a large number of bax-bax homodimers to promote the permeability of the mitochondrial membrane;⁸⁷ on the other hand, it induces the release of the apoptotic factor cytochrome C (Cyt-C).¹⁵⁰ TCM can regulate the tumor cell signaling pathway p53/Bcl-2/Cyt-C/caspase-3 to induce mitochondrial cell apoptosis, thereby exerting an anti-liver cancer effect. 3-kinase/protein kinase B (PI3K/Akt) and mitogen-activated protein kinase (MAPK) are also regulated by mitochondrial signals.^{89,151,152}

Improving the Morphology and Structure of Tumor Blood Vessels

Tumor vessels are structurally and functionally abnormal, lack of a complete basement membrane tightly connected to the cells and a single thin blood vessel wall, leading to an abnormal tumor microenvironment characterized by interstitial hypertension, hypoxia, and acidosis, which in turn hinder delivery and efficacy of anti-tumor treatment.¹⁵³ After the TCM treatment, studies shown that the tumor blood vessels will appear “normalized” within a certain period of time, making tumor blood vessels became regular, the morphology of the pericytes is regular, and improving the hypoxia and acidosis inside tumor.¹⁵⁴ Platelet endothelial cell (EC) adhesion molecule-1 (PECAM-1), also known as cluster of differentiation 31 (CD 31), is an adhesion molecule on the surface of ECs, which accounts for a large part of the connections between actin cytoskeleton of the cells.^{52,155} CD 31 is implicated in angiogenesis, leukocyte migration, and T cell activation has been demonstrated on

immortalized PnMECs. Adenocarcinoma cells and tumor tissue sections showed strong positive expression of CD 31. The study shown that the tumor vascular endothelial cells in the APS-curcumin combination are arranged neatly and closely connected with the carrier group. Pericytes, an integral component of mature blood vessels, wrapping around endothelial cell tubes to provide structural support and generate functional, mature blood vessels and modulate endothelial cell proliferation, survival, and function.^{58,83,156} Compared with vascular cells in normal tissues, pericytes in tumor exhibit altered morphology and epigenetic programming, showing defective blood vessel supporting functions. Clinical data have previously shown that low pericyte coverage is related to reduced patient survival.¹⁵⁷ NG2 is a typical marker of perivascular cells, which contributes to the stabilization of microvessels, the regulation of capillary blood flow, and angiogenesis.¹⁵⁸ In pericytes, the expression of NG2 plays an important role in the localization of pericytes to the endothelial layer and the interaction with endothelial cells. Studies have found that the combined application of Chinese medicine has a synergistic effect on tumor blood vessel maturation.^{53,82} In summary, traditional Chinese medicine can improve the morphology and structure of tumor blood vessels and promote the maturation of tumor blood vessels, which provides a possibility for the normalization of tumor blood vessels in the treatment of liver cancer, and brings a breakthrough for effective anti-cancer treatment.⁴⁸

Endoplasmic Reticulum Stress

The endoplasmic reticulum (ER) stress is recognized as a regulator of homeostasis regarding the accumulation of misfolded proteins in the ER, and maintaining protein balance, which is called protective unfolded protein response (UPR).¹⁵⁹ The main function of UPR is to regulate protein balance through translation attenuation and up-regulation of genes encoding ER chaperone proteins and secretion mechanisms to improve the protein folding ability of ER.¹⁶⁰ However, continuous or intense endoplasmic reticulum stress will drive these unfolded proteins to the cytoplasm, where they are degraded by the ubiquitin-proteasome system (UPS). Once UPS fails, death-related protein kinase (Dapk) will be triggered, and death-related protein kinase (Dapk) is the upstream integrator of apoptosis and autophagy.¹⁶¹ Liu et al¹⁶¹ found that *Polygonum bistorta* aqueous extract (PB) can cause endoplasmic reticulum stress, thereby inhibiting the activity of autophagosomes and proteasomes, inducing Hep3B cell apoptosis. The relationship between autophagy and apoptosis is complex.¹⁶² The accumulation of autophagy will lead to a large amount of cell degradation, leading to cell apoptosis, and autophagy will be negatively regulated by cell apoptosis.⁹⁷ In the process of proteasome formation, the interaction of growth factors, cytoskeleton, and adhesion molecules is considered to be a strategy to change cell migration and adhesion.⁸⁶ In fact, extracts from natural products have the ability to regulate cancer cells. The increase in reactive oxygen species can cause protein damage and degradation, but cancer cells may eliminate reactive oxygen species to fight stress by enhancing their antioxidant capacity. Chinese herbal medicines may reduce the antioxidant capacity of cancer cells, thereby increasing the growth rate of tumors.⁹⁶

Conclusion

Under the guidance of the theory of traditional Chinese medicine, which reflects philosophical principles and embodies large dialectical thought, TCM believes that the human body is a dynamic and complex system, focusing on the influence of the internal and external environments of the human body. After radical resection of HCC, the internal and external environments of patients themselves are destroyed. Modern studies have found that Chinese medicine has passed Immunity, inflammation, and cell proliferation are regulated to reduce the recurrence rate of patients with HCC. However, under the background of modern medicine, there are certain difficulties in the application of traditional Chinese medicine after radical resection of HCC. Therefore, further research should consider investigating the underlying mechanisms of traditional Chinese medicine used in reducing the recurrence of patients with HCC after radical resection to determine which type of TCM or adjunctive treatment is the most effective for improving the survival rate of patients.

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Disclosure

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