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REVIEW

Traditional Chinese medicine for prevention and treatment of hepatocarcinoma: From bench to bedside

Bing Hu, Shuang-Shuang Wang, Qin Du

Bing Hu, Shuang-Shuang Wang, Qin Du, Department of Oncology and Institute of Traditional Chinese Medicine in Oncology, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 200032, China
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Correspondence to: Dr. Bing Hu, Department of Oncology and Institute of Traditional Chinese Medicine in Oncology, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, 725 South Wanping Road, Shanghai 200032, China. beearhu@hotmail.com
Telephone: +86-21-64385700
Fax: +86-21-64398310
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Abstract

Traditional Chinese medicine (TCM) has played a positive role in the management of hepatocarcinoma. Hepatocarcinoma patients may present Qi-stagnation, damp-heat, blood stasis, Qi-deficiency, Yin-deficiency and other TCM syndromes (Zheng). Modern treatments such as surgery, transarterial chemoembolization (TACE) and high intensity focus ultrasound treatment would influence the manifestation of TCM syndromes. Herbs with traditional efficacy of tonifying Qi, blood and Yin, soothing liver-Qi stagnation, clearing heat and detoxifying and dissolving stasis, have been demonstrated to be potent to prevent hepatocarcinogenesis. TCM has been widely used in all aspects of integrative therapy in hepatocarcinoma, including surgical resection, liver transplantation, TACE, local ablative therapies and even as monotherapy for middle-advanced stage hepatocarcinoma. Clinical practices have confirmed that TCM is effective to alleviate clinical symptoms, improve quality of life and immune function, prevent recurrence and metastasis, delay tumor progression, and prolong survival time in hepatocarcinoma patients. The effective mechanism of TCM against hepatocarcinoma is related to inducing apoptosis, autophagy, anoikis and cell senescence, arresting cell cycle, regulating immune function, inhibiting metastasis and angiogenesis, reversing drug resistance and enhancing effects of chemotherapy. Along with the progress of research in this field, TCM will contribute more to the prevention and treatment of hepatocarcinoma.

Key words: Hepatocarcinoma; Traditional Chinese medicine; Prevention; Treatment; Traditional Chinese medicine syndrome (Zheng); Therapeutic principle; Chinese herbal formula; Chinese herb

Core tip: Hepatocarcinoma may present different Traditional Chinese medicine (TCM) syndromes (Zheng). Syndromes are associated with hepatocarcinoma progression and prognosis to a certain degree. Modern technologies have been exploited to elucidate the relation between syndromes and biomedical sciences. Chinese herbs or herbal components have been demonstrated

to be effective to prevent and treat hepatocarcinoma. Contemporary TCM physicians have established some effective herbal formulas and Chinese patent herbal drugs for hepatocarcinoma prevention and treatment.

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INTRODUCTION

Hepatocarcinoma is the sixth most common malignancy and the third principal cause of cancer deaths worldwide[1]. The incidence of hepatocarcinoma is increasing by cause of hepatitis virus infection and other factors[2-4]. Due to latent onset and rapid progression, only a minority of patients with early-stage disease are suitable for potentially curative therapy, *i.e.*, surgical resection or liver transplantation. Treatments for unresectable disease, such as local ablative therapies, transarterial chemoembolization (TACE) and systemic therapy with sorafenib, are essentially palliative[5]. Cancer recurrence is another obstacle to successful treatment, and there is a shortage of preventive means for recurrence. It is important to develop novel approaches for hepatocarcinoma prevention and treatment.

Traditional Chinese medicine (TCM) has played a positive role in the management of hepatocarcinoma[6,7]. TCM has been widely used in all aspects of integrative therapy in hepatocarcinoma, including surgical resection, liver transplantation, chemoembolization, targeted therapy, and even as monotherapy for middle-advanced stage hepatocarcinoma[6-8]. TCM treatment mainly includes multiple herbal therapy and Chinese patent herbal drug therapy. Clinical practices have confirmed that TCM is effective to alleviate clinical symptoms, improve quality of life (QOL), palliate myelosuppression, improve immune function, prevent recurrence and metastasis, delay tumor progression, and prolong survival time[6-9].

TCM therapy is a syndrome differentiation based treatment. Based on TCM pathogenesis, TCM syndrome patterns and different disease stage, TCM physicians employ different therapeutic methods, and prescribe multiple herbs for hepatocarcinoma treatment[10]. The pathogenesis of hepatocarcinoma is related to weakened body defense or deficiency in liver and kidney, liver stagnation, dampness-heat, and blood stasis. Since these pathological factors are also seen in other diseases, contemporary TCM has developed the concept of cancerous toxicity (Ai-Du) to discriminate liver cancer from other common diseases, and underscore the application of anti-cancer therapy to improve overall therapeutic efficacy in hepatocarcinoma[11,12].

During past decades, TCM has been extensively explored to prevent and treat hepatocarcinoma. In this paper, we comprehensively review the experimental and clinical efficacy of TCM against hepatocarcinogenesis and hepatocarcinoma, TCM syndromes in hepatocarcinoma patients and the effective mechanism of TCM in the treatment of hepatocarcinoma, to provide new insights into hepatocarcinoma management.

HEPATOCARCINOMA PREVENTION BY TCM

Disease prevention has long been practiced in TCM. Taking preventive measures against disease or treating before sick had been established as a basic principle for disease control since *Inner Canon of Emperor Huang* (Huang-Di-Nei-Jing) (400 B.C.), Dr. Zhong-Jing Zhang, one of the most prominent Chinese physicians in history, had developed another principle for liver disease prevention in *Synopsis of Golden Cabinet* (Jin-Gui-Yao-Lüe) (A.D 200 - 210). Dr. Zhang observed that liver diseases tend to spread to the spleen, and proposed that the spleen-Qi should be reinforced before it is affected. Hepatocarcinoma prevention by Chinese herbs or related products has been extensively studied in recent decades.

Classical herbal formulas

Chinese herbal formula or Chinese herbal compound prescription is the most representative application form of Chinese herbs. It has been shown that some classical herbal formulas have preventive effects against hepatocarcingenesis. Ren-shen-bie-jia-jian, a formula for nourishing Qi and dissolving stasis, is effective in inhibiting hepatocarcinogenesis and down-regulation of transforming growth factor-β type Ⅱ receptor (TGF-β ⅡR)[13]. Xiao-chai-hu-tang, a formula used for soothing liver-Qi stagnation, may inhibit N-nitrosomorpholine (NNM) induced hepatocarcinogenesis and increase the proportion of helper T lymphocytes in rats[14]. Shi-quan-da-bu-tang, a classical formula for tonifying Qi-blood, inhibits NNM induced hepatocarcinogenesis and increases interleukin-2 (IL-2) receptor-positive lymphocytes in rats[15]. However, the more exploited and studied are modern formulas.

Liver and/or kidney-tonifying herbal formulas

According to TCM theory, the liver and kidney share the same origin, and thus tonifying liver and/or kidney is frequently used to prevent hepatocarcinoma. Nourishing Yin Decoction, a formula for tonifying liver Yin, may inhibit aflatoxin B1 (AFB1) induced hepatocarcinogenesis[16]. A-L tonic capsule, a tonifying liver and kidney Yin and nourishing Qi based Chinese patent drug for improving the immune system in cancer patients, may reduce DNA content and improve its distribution in rat hepatocarcinogenesis induced by diethylnitrosamine (DEN)[17]. Bu Shen Prescription, a formula composed of eight herbs for tonifying kidney, inhibits DEN induced hepato-

carcinogenesis in rats[18].

Liu *et al*[19] established Fu-zheng-hua-yu formula for tonifying kidney and dissolving stasis, and demonstrated that it may inhibit hepatocarcinogenesis and induce cell cycle S phase arrest in DEN treated rat models. Fu-zheng-hua-yu formula has been developed as a Chinese patent drug for liver fibrosis treatment. Huqi San, a formula for tonifying kidney and nourishing Qi, inhibits the over-expression of c-jun, c-fos and c-myc oncogenes and liver preneoplastic lesions induced by DEN[20,21].

Spleen-strengthening herbal formulas

Strengthening spleen is an important principle for hepatocarcinoma prevention. Ganfujian, a formula composed of dietary and medicinal Chinese herbs for strengthening spleen, has showed effects in inhibiting hepatocarcinogenesis, and down-regulation of CDK4 (cyclin-dependent kinase 4), cyclin D1 and PCNA (proliferating cell nuclear antigen) in DEN induced hepatic carcinogenesis in rats[22]. Qiu *et al*[23] have established an herbal recipe for strengthening spleen, regulating Qi, removing heat, and softening hard lumps and resolving phlegm (SRRS). SRRS recipe has been demonstrated to have preventive effects against DEN induced hepatocarcinogenesis[23]. Jianpi Jiedu Recipe, an herbal formula for strengthening spleen and detoxification, has been showed to be effective in inhibiting DEN induced hepatocarcinogenesis, down-regulating miR-199a and Phosphatidylinositol-4,5-bisphosphate 3-kinaseV-akt murine thymoma viral oncogene homolog (PI3K/AKT), and up-regulating p70s6k[24,25].

Detoxifying herbal formulas

In addition to tonifying treatments, eliminating pathogenic factors is another important principle for hepatocarcinoma prevention. Removing Toxic Heat Decoction, a formula based on detoxifying and tonifying liver Yin, may inhibit AFB1 induced hepatocarcinogenesis[16]. Gao *et al*[26] evaluated Gan-Zheng oral solution, a formula for detoxification and dissolving stasis, in a DEN induced rat model and demonstrated that it is effective in inhibiting hepatocarcinogenesis and down-regulating intercellular adhesion molecule 1 (ICAM-1)[26]. Zao-Lian mixture, a formula for detoxification, dissolving stasis, strengthening spleen, and soothing liver, may inhibit hepatocarcinogenesis and protect liver function[27]. Sb/Bs remedy, containing *Scutellaria baicalensis* Georgi (Sb) and *Bupleurum scorzonerifolfium* Willd (Bs), suppressed N-nitrosobis(2-oxopropyl)amine (BOP) induced liver tumours, increased serum tumor necrosis factor (TNF)-alpha and TGF-beta1, decreased 8-OHdG expression, and increased caspase-3 and apoptosis[28].

Stasis-dissolving and other herbal formulas

Professor Fang's group has investigated different TCM treatments in DEN mediated hepatocainogenesis, and found that the more efficient treatments are, in order, promoting circulation and removing stasis, clearing heat and detoxifying, and strengthening spleen. All those treatments up-regulated GTPase-activating protein expression and down-regulated Ras expression. Expression of growth factor receptor-bound protein 2 and Raf 1, and son of sevenless was inhibited by those treatments, respectively[29-31]. Herbal compound 861, a formula composed of herbs with dissolving stasis and nourishing Qi efficacy, prevents 2-acetylaminofluorene (2-AAF) induced hepatocarcinogenesis in rats[32]. A new anti-tumor formula with tonifying Qi, soothing liver and dissolving stasis effects inhibits hepatocarcinogenesis induced by HBV and AFB1 accompanied by superoxide dismutase (SOD) and glutathione S-transferase (GST) activation and decreased malondialdehyde (MDA)[33].

Tonic herbs

Ginseng, one of the most frequently used herbs for tonifying Qi, has been reported to be effective in inhibiting DEN induced hepatocellular carcinoma in rats[34]. Dang-Gui (*Angelica sinensis*), a common used blood tonic, is potent to inhibit AFB1 induced mutagenicity in Ames test and hepatocarcinogenesis induced by AFB1[35,36]. Ying-tonifying herbs such as Nü-Zhen-Zi (*Ligustrum lucidum* Ait.), Tian-Dong (*Asparagus cochinchinensis*), Bai-He (*Lilium brownii*) and Shan-Zhu-Yu (*Cornus officinalis*) are efficient to inhibit AFB1 induced mutagenicity in Ames test[36]. Cao-Cong-Rong (*Boschniakia rossica*), an herb with traditional efficacy of Yang-tonifying, may inhibit DEN induced hepatocarcinogenesis, increase SOD and GSH-PX (glutathione peroxidase), and down-regulate expression of MDA, GST and mutant p53 and p21 proteins[37,38].

Heat-clearing herbs

Ban-Zi-Lian (*Sculellaria barbata*), an herb with traditional efficacy of clearing heat and detoxifying, has been widely used as an anti-cancer herb. Ban-Zi-Lian has been reported to be able to inhibit experimental hepatocarcinoma and relieve hepatic injures in DEN treated rats[39]. Tu-Fu-Ling (*Smilax glabra* Roxb.), another commonly used clearing heat and detoxifying herb, inhibits hepatocarcinogenesis induced by AFB1[35]. Penta-acetyl geniposide, a component of Zhi-Zi (*Gardenia jasminoides* Ellis), may protect rats from AFB1 induced hepatocarcinogenesis[40]. Berberine, a component of Huang-Lian (*Coptis chinensis* Franch.) or Huang-Bai (*Phellodendron chinense* Schnied.), inhibits hepatocyte proliferation and inducible nitric oxide synthase expression, decreases cytochrome P450 content, inhibits activities of cytochrome P450 2E1 (CYP2E1) and CYP1A2 in DEN plus phenobarbital treated rats[41]. Yin-Chen-Hao (*Artemisia capillaris* Thunb.), an herb for clearing heat, inducing urination and removing jaundice, has been reported to be effective in inhibiting AFB1 induced mutagenicity in Ames test[42].

Stasis-dissolving herbs

Dissolving stasis is another principle for hepatocarcinoma

prevention. Dan-Shen (*Salvia miltiorrhiza* Bunge) may inhibit AFB1 mediated mutagenicity and hepatocarcinogenesis, decrease AFB1-DNA adducts formation and AFB1-induced oxidative DNA damage, and induce glutathione S-transferase Yc-2 expression[35,36,43]. Jiang-Huang (*Curcuma longa* Linn) has beneficial effects on the early and late stages of liver pathogenesis, prevents and delays liver carcinogenesis, and may be related to decreased expression of hepatitis B virus X protein (HBx) and increased expression of p-p53, p21 and cyclin D1 in livers of HBx transgenic mice[44]. Shan-Qi (*Panax notoginseng*), an herb used for hemostasis and dissolving stasis, has been showed to be effective to inhibit DEN induced hepatocarcinogenesis and angiogenesis accompanied by down-regulation of angiopoietin-2, tunica internal endothelial cell kinase 2, hypoxia inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF)[45].

Other herbs

Wu-Wei-Zi (*Schisandra chinensis*), commonly used for inducing astringency, could inhibit AFB1 induced mutagenicity in Ames test and hepatocarcinogenesis induced by AFB1[35,36]. Gomisin A, an ingredient of Wu-Wei-Zi, is effective to inhibit 3'-methyl-4-dimethylaminoazobenzene induced hepatocarcinogenesis by enhancing the excretion of the carcinogen from the liver and by reversing the normal cytokinesis[46]. Other herbs, such as Bai-Ji (*Bletilla striata*), which may inhibit FAB1 induced hepatocarcinogenesis, Shan-Zha (*Crataegus pinnatifida*), Yi-Yi-Ren (*Coix lacryma-jobi* L.), Xing-Ren (*Prunus armeniaca*) and Wu-Mei (*Prunus mume*), which may inhibit AFB1 induced mutagenicity in Ames test[35,36].

Clinical prevention against hepatocarcinogenesis

Current treatments for hepatocarcinoma are less than satisfactory. It is important to prevent hepatocarcinogenesis in high risk populations. Jian-Pi-Huo-Xue Formula based herbal treatment has been demonstrated to be effective to inhibit hepatocarcinogenesis in patients with hepatitis, hepatic cirrhosis and low level of AFP[47]. Dan-Shen (*Salvia miltiorrhiza* Bunge) is potent to protect male individuals from hepatocarcinogenesis in a high incidence area of hepatocarcinoma[48]. In Japan, Sho-saiko-to (TJ-9) (Xiao-chai-hu-tang) has been demonstrated to be potent to prevent heapto-carcinogenesis in patients with cirrhosis, particularly in patients without HBs antigen[49].

Taken together, contemporary TCM physicians have adopted classic TCM theory and principles for hepatocarcinoma prevention study, developed A-L tonic capsule, Fu-zheng-hua-yu capsule, Ganfujian, Gan-Zheng oral solution, Herbal compound 861 and other effective herbal formulas/drugs, and confirmed that Nü-Zhen-Zi, Ban-Zi-Lian, Yin-Chen-Hao, Dan-Shen, Wu-Wei-Zi and other herbs could inhibit hepatocarcinogenesis. It is regrettable that there are no more studies on hepatitis virus induced hepatocarcinogenesis models. Related studies will promote TCM to contribute more to protect high-risk individuals from hepatocarcinogenesis. Herbal formulas for hepatocarcinoma prevention are listed in Table 1.

TCM SYNDROMES IN HEPATOCARCINOMA

TCM syndrome (Zheng) is pathological status that integrates information from clinical symptoms, etiology, disease location and character, tongue picture and TCM theory, and serves as the basis for herbal medication. The clinical manifestation of liver cancer is complex and different patients or different stage of disease may present different TCM syndromes.

Syndrome differentiation in hepatocarcinoma

In 294 patients preliminarily diagnosed with primary liver cancer, Zhao *et al*[50] found the early symptoms were more observed in the liver and biliary system and digestive tract system. Except for 23.5% of patients without any TCM syndrome, the frequently observed syndromes include dampness, blood-stasis, Qi-stagnation, Qi-deficiency, blood-deficiency, heat, Yang-asthenia and Yin-asthenia. One hundred and eleven cases presented with single syndrome, 76 cases with two combined syndromes, 31 cases with three combined syndromes, 6 cases with four combined syndromes and 1 case with five combined syndromes[50].

In another study, the common syndromes observed in liver cancer patients include blood stasis, spleen-Qi-deficiency, liver-Qi stagnation, spleen deficiency and dampness blocking, disharmony of liver and stomach, dampness-heat of spleen and stomach, liver-Yin-deficiency and kidney-Yin-deficiency. Liver-Qi stagnation and spleen-Qi-deficiency can be found in patients from stages Ⅰ to Ⅲ. Main syndromes in stage Ⅱ are blood stasis, Qi-stagnation, Qi-deficiency and damp-heat. While in stage Ⅲ, Qi-deficiency, Yin-deficiency, blood stasis, Qi-stagnation and retention of water are the most common syndromes. The average numbers of syndromes in stages Ⅰ, Ⅱ and Ⅲ are 2.03, 3.47 and 4.99, respectively. These observations suggest that syndromes are more complicated along with disease progression, and Qi stagnation, blood stasis, Qi-deficiency and Yin-deficiency are the basic syndromes in liver cancer[51,52].

In Guangzhou area, Wang *et al*[53] have found that TCM syndromes distributed in liver cancer patients include spleen deficiency, Qi stagnation, blood stasis and damp-heat. Two overlapped syndromes were observed in 43.5% of patients and 19.9% for three. The overlapped syndromes in patients with stage Ⅱ disease are spleen deficiency and Qi stagnation, Qi stagnation and blood stasis, spleen deficiency and damp-heat, and liver and spleen deficiency. The overlapped syndrome in patients with stage Ⅲ disease is liver and kidney-Yin-deficiency[53].

Syndromes are related to prognosis and QOL to some extent. Yang *et al*[54] analyzed relation between syndrome and survival time. They found that the median survival

Table 1 Herbal formulas for hepatocarcinoma prevention

Herbal formula	Therapeutic principles	Herbs	Models/patients	Effects	Targets/events	Ref.
Ren-shen-bie-jia-jian	Tonifying Qi and dissolving stasis	Ren-Shen (*Panax ginseng*), Bie-Jia (Carapax trionycis), Tao-Ren (Peach seed) and other herbs	DMN induced hepatic precancerous lesion in rats	Inhibit hepatocarcinogenesis	Down-regulation of TGF-βⅡR	[13]
Xiao-chai-hu-tang	Soothing liver-Qi stagnation	Chai-Hu (*Bupleurum chinense*), Huang-Qin (*Scutellaria baicalensis* Georgi), Sheng-Jiang (*Zingiber officinale*), Ban-Xia (*Pinellia ternata*), Da-Zao (*Ziziphus jujuba*), Ren-Shen (*Panax ginseng*), Gan-cao (*Glycyrrhiza uralensis*)	NNM induced hepatocarcinogenesis in rats; patients with cirrhosis	Inhibit hepatocarcinogenesis, prevent hepatocarcinogenesis in patients	Increase helper T lymphocytes	[14,49]
Shi-quan-da-bu-tang	Tonifying Qi-Blood	Ren-Shen (*Panax ginseng*), Bai-Zhu (*Atractylodes macrocephala* Koidz.), Fu-Ling (Poria cocos), Gan-cao (*Glycyrrhiza uralensis*), Chuan-Xiong (*Ligusticum chuanxiong*), Dang Gui (*Angelica sinensis*), Shu-Di-Huang (*Rehmannia glutinosa*), Bai-Shao (*Paeonia lactiflora*), Huang Qi (*Astragalus membranaceous*), Rou-Gui (*Cinnamomum cassia* Presl)	NNM induced hepatocarcinogenesis in rats	Inhibit hepatocarcinogenesis	Increase IL-2 receptor-positive lymphocytes	[15]
Nourishing Yin Decoction	Tonifying liver Yin	Bei-Sha-Shen (*Glehnia littoralis*), Dang-Gui (*Angelica sinensis*), Bai-Shao (*Paeonia lactiflora*), Gou-Qi (*Lycium barbarum*), *etc.*	AFB1 induced hepatocarcinogenesis in rats	Inhibit hepatocarcinogenesis	Unknown	[16]
Removing Toxic Heat Decoction	Detoxifying and tonifying liver Yin	Ban-Zi-Lian (*Sculellaria barbata*), Ban-Bian-Lian (*Lobelia chinensis* Lour.), Mo-Han-Lian (*Eclipta prostrata*), Gu-Ya (rice sprout), *etc.*	AFB1 induced hepatocarcinogenesis in rats	Inhibit hepatocarcinogenesis	Unknown	[16]
A-L tonic capsule	Tonifying liver-Yin and nourishing Qi	Nü-Zhen-Zi (*Ligustrum lucidum* Ait.) and Huang-Qi (*Astragalus membranaceous*)	DEN induced hepatocarcinogenesis in rats	Inhibit DNA content and improve DNA distribution	Unknown	[17]
Bu Shen formula	Tonifying kidney	Ba-Ji-Tian (*Morinda officinalis*), Tu-Si-Zi (*Cuscuta chinensis* Lam), Qing-Pi (*Cuscuta chinensis* Lam) and other herbs	DEN induced hepatocarcinogenesis in rats	Inhibit hepatocarcinogenesis	Unknown	[18]
Fu-zheng-hua-yu formula	Strengthening body resistance and dissolving stasis	Dong-Chong-Xia-Cao (*Cordyceps sinensis*), Tao-Ren (Peach seed), Dan-shen (*Salvia miltiorrhiza*) and other herbs	DEN induced hepatocarcinogenesis in rats	Inhibit hepatocarcinogenesis	Inhibit cell cycle S phase	[19]
Huqi San	Tonifying kidney, nourishing Qi, and dissolving stasis	Hu-Ji-Sheng (*Viscum coloratum*), Huang-Qi (*Astragalus membranaceus*), Yu-Jin (*Radix Curcumae*), Dan-shen (*Salvia miltiorrhiza*) and other herbs	DEN and 2-acetylaminofluorene induced hepatocarcinogenesis in rats	Inhibit hepatocarcinogenesis	Down-regulation of c-jun, c-fos and c-myc, up-regulation of G-6-Pase, SDH and ATPase	[20,21]
Ganfujian	Strengthening spleen	Shan-Yao (Rhizoma Dioscoreae), Shan-Zha (Fructus Crataegi) and Da-Zao (Fructus Ziziphi Jujubae)	DEN induced hepatocarcinogenesis in rats	Inhibit hepatocarcinogenesis	Down-regulation of CDK4, cyclin D1 and PCNA	[22]
SRRS recipe	Strengthening spleen, regulating Qi, removing heat, and softening hard lumps and resolving phlegm	Tai-Zi-Shen (*Pseeudostellaria heterophylla*), Zhu-Zi-Shen (*Panax japonicus*), Bai-Zhu (*Atractylodes macrocephala* Koidz.), Fu-Ling (*Poria cocos*), Sheng-Mu-Li (raw oyster shell) other herbs	DEN induced hepatocarcinogenesis in rats	Inhibit hepatocarcinogenesis	Unknown	[23]
Jianpi Jiedu Recipe	Strengthening spleen and detoxifying	Huang-Qi (*Astragalus membranaceous*), Bai-Zhu (*Atractylodes macrocephala* Koidz.), Zhu-Ling (*Polyporus umbrellatus*), Ba-Yue-Zha (*Akebia trifoliata*), Shi-Jian-Chuan (*Salvia chinensis*), Ye-Pu-Tao-Teng (Wild grape stem), Yi-Yi-Ren (*Coix lacryma-jobi L.*) other herbs	DEN induced hepatocarcinogenesis in rats	Inhibit hepatocarcinogenesis	Down-regulating miR-199a and AKT/PI3K, and up-regulating p70s6k	[24,25]
Gan Zheng oral solution	Detoxifying and dissolving stasis	Ban-Zi-Lian (*Sculellaria barbata*), Bai-Hua-She-She-Cao (*Hedyotis diffusa* Willd.), San-Leng (*Sparganium stoloniferum*), E-Zhu (*Curcuma kwangsiensis* or *Curcuma phaeocaulis* or *Curcuma wenyujin*) and other herbs	DEN induced hepatocarcinogenesis in rats	Inhibit hepatocarcinogenesis	Down-regulating ICAM-1	[26]
Zao Lian mixture	Detoxifying, dissolving stasis, strengthening spleen, and soothing liver	Zao-Xiu (*Paris Polyphylla*), Ban-Zi-Lian (*Sculellaria barbata*), Hu-Zhang (*Polygonum cuspidatum*), Jiang-Huang (*Carcuma longa*), Huang-Qi (*Astragalus membranaceous*), Bai-Zhu (*Atractylodes macrocephala* Koidz.), Fu-Ling (*Poria cocos*), *etc.*	DEN induced hepatocarcinogenesis in rats	Inhibit hepatocarcinogenesis	Improve liver function	[27]

Sb/Bs Remedy	Clearing heat and discharging fire, eliminating dampness and detoxifying, and soothing liver	Huang-Qin (*Scutellaria baicalensis* Georgi) and Chai-Hu (*Bupleurum scorzonerifolfium* Willd)	N-nitrosobis(2-oxopropyl)amine-induced hepatocellular carcinoma in Syrian hamsters	Inhibit hepatocarcinogenesis	Increase TNF-alpha, TGF-beta1, caspase-3 and apoptosis, decrease 8-OHdG expression	[28]
Qing Re Fang	Clearing heat and detoxifying	Ban-Zi-Lian (*Sculellaria barbata*), Bai-Hua-She-She-Cao (*Hedyotis diffusa* Willd.) and Pu-Gong-Ying (*Taraxacum mongolicum*)	DEN induced hepatocarcinogenesis in rats	Inhibit hepatocarcinogenesis	Up-regulate GAP, down-regulate Ras and Raf1	[29-31]
Huo Xue Fang	Promoting circulation and removing stasis	Chai-Hu (*Bupleurum chinense*), Dan-Shen (*Salvia miltiorrhiza*), Chi-Shao (*Paeonia lactiflora* Pall. or *P. veitchii* Lynch), Ba-Yue-Zha (Caulis Akebiae), Yin-Chen-Hao (*Artemisia capillaris* Thunb.), Yu-Jin (Radix Curcumae)	DEN induced hepatocarcinogenesis in rats	Inhibit hepatocarcinogenesis	Up-regulate GAP, down-regulate Ras, Grb-2 and Raf 1	[29-31]
Jian Pi Fang	Strengthening spleen	Huang-Qi (*Astragalus membranaceus*), Bai-Zhu (*Atractylodes macrocephala* Koidz.), Bai-Shao (*Paeonia lactiflora*), Yi-Yi-Ren (Semen Coicis), Shen-Qu (medicated leaven), Ban-Xia (*Pinellia ternata*) and Fu-Ling (*Poria cocos*)	DEN induced hepatocarcinogenesis in rats	Inhibit hepatocarcinogenesis	Up-regulate GAP, down-regulate Ras and SOS	[29-31]
Herbal Compound 861	Dissolving stasis and tonifying Qi	Dan-Shen (*Salvia miltiorrhiza*), Huang-Qi (*Astragalus membranaceus*), Ji-Xue-Teng (*Spatholobus suberectus*) and other herbs	DEN and 2-acetylaminofluorene induced hepatocarcinogenesis in rats	Inhibit hepatocarcinogenesis	Unknown	[32]
New Anti-tumor formula	Tonifying qi, soothing liver and dissolving stasis	Huang-Qi (*Astragalus membranaceus*), Chai-Hu (*Bupleurum chinense*), E-Zhu (*Curcuma kwangsiensis* or *Curcuma phaeocaulis* or *Curcuma wenyujin*) and other herbs	AFB1 and HBV induced hepatocarcinogenesis in rats	Inhibit hepatocarcinogenesis	Activate SOD and GST, decrease MDA	[33]
Jian-Pi-Huo-Xue Formula	Strengthening spleen and dissolving stasis	Huang Qi (*Astragalus membranaceous*), Chi-Shao (*Paeonia anomala*), Dang-Shen (*Codonopsis pilosula*), Dang-Gui (*Angelica sinensis*), E-Zhu (*Curcuma kwangsiensis* or *Curcuma phaeocaulis* or *Curcuma wenyujin*) and other herbs	Patients with hepatitis, hepatic cirrhosis and low level of AFP	Prevent hepatocarcinogenesis in patients	Unknown	[47]

DMN: Dimethylnitrosamine; NNM: N-nitrosomorpholine; AFB1: Aflatoxin B1; DEN: Diethylnitrosamine; HBV: Hepatitis B virus; AFP: Radiofrequency ablation; TGF-βⅡR: Alpha fetoprotein; transforming growth factor-β type Ⅱ receptor; IL-2: Interleukin-2; PCNA: Proliferating cell nuclear antigen; CDK4: Cyclin-dependent kinase 4; PI3K/AKT: Phosphatidylinositol-4,5-bisphosphate 3-kinaseV-akt murine thymoma viral oncogene homolog; ICAM-1: Intercellular adhesion molecule 1; TNF: Tumor necrosis factor; Grb-2: Growth factor receptor-bound protein 2; GAP: GTPase-activating protein; SOS: Son of sevenless; SOD: Superoxide dismutase; GST: Glutathione S-transferase; MDA: Malondialdehyde.

times in patients with liver-stagnation and spleen-deficiency, Qi stagnation and blood stasis, damp-heat, dampness and blood stasis, liver and kidney-Yin-deficiency were 14.77 mo, 6.13 mo, 5.27 mo, 4.78 mo and 0.80 mo, respectively[54]. Wan *et al*[55] reported the QOL in patients with sthenia syndrome, such as Qi stagnation, blood stasis and damp-heat, was relatively better than those with asthenia syndrome including Qi-deficiency, Yin-deficiency and blood deficiency[55].

The influence of modern treatment on syndromes in hepatocarcinoma

In addition to disease, treatments such as surgery, TACE and high intensity focus ultrasound (HIFU) treatment would influence syndrome pattern. Before surgery, a large proportion of patients presented blood stasis (22.1%) and damp-heat (20.9%). After operation, blood stasis syndrome decreased while spleen deficiency syndrome increased. The most common syndromes in postoperative patients are damp-heat (21.8%) and spleen deficiency (21.0%)[56]. In a tongue picture study, Ye *et al*[57] reported that the tongues of blood stasis, dampness and Qi-deficiency pattern were commonly observed during the perioperative period of liver cancer, but the tongues of Yin asthenia generating intrinsic heat were increased within 5 d after surgery[57].

TACE is another principal treatment for liver cancer and has been demonstrated to be able to impair Yin, and generate heat and dampness in liver cancer patients[58]. Before interventional treatment, the commonly observed TCM syndromes are liver stagnation, spleen deficiency, damp-heat, blood stasis and Yin-deficiency[59]. After interventional treatment, damp-heat syndrome was increased, and liver stagnation and spleen deficiency decreased. Simultaneous TCM treatment could restore these syndrome changes[60]. In another report, Qi-deficiency and dampness were worsened, while the liver-Qi stagnation and blood stasis were alleviated after TACE. These changes suggest local disease improvement and general impairment[61].

In a systematic observation, Zhang *et al*[62] reported that the syndromes before TACE treatment were blood stasis (86.8%), excess-heat (68.9%), Qi stagnation (58.5%), Qi-deficiency (58.5%), Yin-deficiency (56.6%), blood deficiency (28.3%), Yang-deficiency (17.0%), and fluid and damp syndrome (14.2%). TACE treatment increased Qi-deficiency and Yang-deficiency syndrome. The syndromes found in post-TACE patients were blood stasis (84.0%), Qi-deficiency (82.1%), excess-heat (80.2%), Qi stagnation (49.1%), Yin-deficiency (46.2%), blood deficiency (39.6%), Yang-deficiency (30.2%), and fluid and damp syndrome (18.9%)[62].

HIFU treatment, an important method for liver cancer therapy, may also affect syndrome distribution. It has been reported that syndromes observed before HIFU treatment are Qi-deficiency, blood deficiency, Yin-deficiency, Qi stagnation, blood stasis and dampness. HIFU treatment could relieve Qi stagnation and blood stasis, and aggravate Qi-deficiency and Yin-deficiency[63].

Molecular insights into syndromes in hepatocarcinoma

Contemporary TCM has studied liver cancer syndrome by methods of biomedical science. By using a metabonomics method, Chen *et al*[64] found that amino acid metabolism, lipid metabolism, glycometabolism and energy metabolism are unbalanced or weak in liver cancer patients with Yang-deficiency. Metabolites, including very-low-density lipoprotein/low-density lipoprotein, isoleucine, lactate, lipids, choline and glucose/sugars, were decreased and may be potential biomarkers for diagnosis of Yang-deficiency syndrome in liver cancer patients[64].

Serum protein is a potential source for syndrome study. By using surface enhanced laser desorption ionization time of flight mass spectrometry, Yang *et al*[65] found serum proteins with mass-to-charge ratios (M/Z) of 6589 and 4182 Da (dalton) were down-regulated in liver stagnation syndrome, that with an M/Z of 5710 Da was down-regulated in damp-heat syndrome, that with an M/Z of 6992 Da was down-regulated in Yin-deficiency syndrome, while those with M/Z of 5816 Da and 4297 Da were up-regulated in spleen deficiency and blood stasis syndrome, respectively[65]. Huang *et al*[66] reported that proteins with M/Z of 8576 Da (cytochrome C6) and 8780 Da (cytochrome c oxidase assembly factor 5) were over-expressed in serum from patients with liver stagnation syndrome[66].

By means of GeneChip, Weng *et al*[67] reported that 615 mRNAs were differentially expressed in peripheral blood mononuclear cells from liver cancer patients with liver-kidney Yin-deficiency syndrome. These genes are related to *GO* (gene ontology) of anti-apoptosis, regulation of cell cycle and transmembrane transport, and 26 kyoto encyclopedia of genes and genomes pathways. Among these genes, SEC62 [SEC62 homolog (S. cerevisiae)], cyclin B1 and baculoviral IAP repeat containing 3 (BIRC3) were significantly down-regulated in patients with syndrome of liver-kidney Yin-deficiency compard with those without[67].

TCM syndrome is closely associated with the stage of disease. Su *et al*[68,69] explored the relationship between syndrome differentiation and metastasis potential of hepatocarcinoma cells. The percentage of metastasis in patients was ranked from high to low as follows: liver and kidney-Yin-deficiency, Qi stagnation and blood stasis, damp-heat, and liver stagnation and spleen deficiency, and was related to up-regulation of β-catenin and down-regulation of E-cadherin and matrix metalloproteinase-2 (MMP2)/tissue inhibitor of metalloproteinase-2[68,69].

In addition to clinical studies, it has been confirmed that mouse models can be used for syndrome exploration[70]. Pan *et al*[71] studied gene expression in the adrenal glands of H22 liver cancer bearing mice. In toxicity accumulation and Qi-deficiency syndrome (early stage), xanthine dehydrogenase and other 18 genes were up-regulated, while eukaryotic translation elongation factor 1 alpha 2 and other 8 genes were down-regulated. In Yang-Qi-deficiency syndrome (middle stage), enolase 3 (beta muscle) and other 11 genes were up-regulated, while solute carrier family 32 (GABA vesicular transporter) and other 10 genes were down-regulated. In Qi-Yin-Yang-deficiency syndrome (advanced stage), albumin and other 29 genes were up-regulated, while ATPase, Na^+/K^+ transporting, beta 2 polypeptide and other 5 genes were down-regulated. S100 calcium binding protein A8 (calgranulin A) and other 11 genes were gradually up-regulated from early stage to advanced stage[71].

CLINICAL STUDY OF TCM FOR HEPATOCARCINOMA TREATMENT

TCM has been widely used for liver cancer treatment in combination with surgery, TACE, radiofrequency ablation (RFA), microwave ablation (MWA), HIFU and target therapy, or as monotherapy for disease control and/or alleviating symptoms. TCM have been demonstrated to be effective to inhibit tumor growth, prolong survival time, ameliorate symptoms, and improve QOL and immune function in hepatocarcinoma patients (Table 2). Related studies will further improve clinical efficacy of TCM and benefit more to hepatocarcinoma patients.

TCM in combination with surgery

Surgery is one of the most important treatments for hepatocarcinoma. TCM has been proved potent to prevent recurrence and metastasis after the surgery. Treatment with Jiedu Granule and Cinobufacini injection may postpone tumor recurrence and metastasis, and prolong survival time in postoperative patients with hepatocarcinoma[72]. Long-term use of Ruanjianhugan tablets could prolong overall survival time in postoperative patients with small hepatocarcinoma[73]. Treatment with Jiedu xiaozheng yin for 7 d before surgery and Fuzheng

Table 2 Clinical study of traditional Chinese medicine for hepatocarcinoma treatment

Treatments	TCM therapeutic principles	Herbs/herbl formula	Disease	No. of patients	Effects	Ref.
Surgery, Jiedu Granule and Cinobufacini Injection	Detoxifying and dissipating mass	Jiedu Granule: Shi-Jian-Chuan (*Salvia chinensis*), Mao-Ren-Shen (*Actinidia valvata*), Yi-Yi-Ren (*Semen Coicis*), Shan-Zha (*Fructus Crataegi*), Shen-Qu (*Massa Medicata Fermentata*), *etc.*	Hepatocellular carcinoma after surgical resection	120	Postpone tumor recurrence and metastasis, prolong survival time	[72]
Surgery, Ruanjianhugan Tablets	Detoxifying, dispersing stasis, tonifying Qi and Yin	Ku-Shen (*Sophora flavescens* Ait.), Xia-Ku-Cao (*Prunella*), Hu-Zhang (*Polygonum cuspidatum*), Nü-Zhen-Zi (*Ligustrum lucidum* Ait), Huang-Qi (*Astragalus membranaceus*), *etc.*	Small hepatocellular carcinoma after surgical resection	399	Prolong overall survival time	[73]
Surgery, Jiedu Xiaozheng Yin and Fuzheng Yiliu Recipe	Detoxifying and dissipating mass, tonifying Qi and Yin	Jiedu Xiaozheng Yin: Bai-Hua-She-She-Cao (*Hedyotis diffusa* Willd), Shan-Ci-Gu (*Pseudobulbus Cremastrae*), Ku-Shen (*Sophora flavescens* Ait.), *et al*. Fuzheng Yiliu Recipe: Huang-Qi (*Astragalus membranaceus*), Nü-Zhen-Zi (*Ligustrum lucidum* Ait), Shan-Yao (*Dioscorea opposita*), *etc.*	Stage Ⅲ hepatocarcinoma before and after surgical resection	72	Prolong survival time and prevent recurrence	[74]
JDF Granule and TACE	Detoxifying and dispersing stasis	Mao-Ren-Shen (*Actinidia valvata*), Shi-Jian-Chuan (*Salvia chinensis*), Shan-Ci-Gu (*Pseudobulbus Cremastrae*), Ji-Nei-Jin (*gizzard membrane of Gallus gallus domesticus*)	Unresectable hepatocellular carcinoma	165	Prolong survival time	[75]
Shentao Ruangan Pill and TACE	Detoxifying, dispersing stasis, tonifying Qi and Yang	Yin-Chen-Hao (*Artemisia capillaris* Thunb.), Bai-Hua-She-She-Cao (*Hedyotis diffusa* Willd.), Ban-Zi-Lian (*Scutellaria barbata*), E-Zhu (*Curcuma kwangsiensis* or *Curcuma phaeocaulis* or *Curcuma wenyujin*), Ren-Shen (*Panax ginseng*), *etc.*	Middle-advanced stage large hepatocarcinoma	85	Prolong survival time	[76]
Ganai No. I and No. II and TACE	Tonifying Qi and Yin, detoxifying and dissipating mass	Ganai No. Ⅰ: Dang-Shen (*Codonopsis pilosula*), Huang Qi (*Astragalus membranaceous*), Nü-Zhen-Zi (*Ligustrum lucidum* Ait), E-Zhu (*Curcuma kwangsiensis* or *Curcuma phaeocaulis* or *Curcuma wenyujin*), Bai-Hua-She-She-Cao (*Hedyotis diffusa* Willd.), *etc.* Ganai No. Ⅱ: Xue-Jie (*Daemonorops draco* BL.), Ru-Xiang (*Boswellia carterii* Birdw), Mo-Yao (*Commiphpra myrrha* Engl.), Zao-Xiu (*Paris polyphylla* Sm.), Long-Kui (*Solanum nigrum* L.), *etc.*	Middle-advanced stage liver cancer	60	Prolong survival time, prevent recurrence and alleviate HACE induce leukocytopenia	[77]
Jinlong Capsule and TACE or RFA	Detoxifying and dissipating mass	Tian-Long (Gecko), Jin-Qin-Bai-Hua-She (Multibanded krait), Qi-She (Long-nosed pit viper)	Unresectable hepatocarcinoma	98, 76	Enhance short-term effect of TACE and improve quality of life; enhance RFA effects, reduce RFA induced liver injury, improve QOL and immune function	[78,89]
Syndrome differentiation based TCM therapy and TACE	Syndrome differentiation based TCM therapy	Xiao-Yao-San/Chai-Hu-Shu-Gan-San, Hua-Yu-Xiao-Liu-Tang, Long-Dan-Xie-Gan-Tang, Yi-Guan-Jian + Liu-Wei-Di-Huang-Wan	Middle-advanced stage hepatocarcinoma	67	Enhance short-term efficacy and reduce adverse effect of TACE, improve immune function and QOL	[79]
Shelian Capsule and TACE	Detoxifying, dissipating mass, tonifying Qi	Bai-Hua-She-She-Cao (*Hedyotis diffusa* Willd.), Ban-Zi-Lian (*Scutellaria barbata*), Hu-Zhang (*Polygonum cuspidatum*), Dan-shen (*Salvia miltiorrhiza* Bge.), Ren-Shen (*Panax ginseng*), *etc.*	Early middle and advanced stage hepatocarcinoma	120	Enhance short-term efficacy of TACE, improve immune function and QOL	[80]
Matrine Injection and TACE	Clearing heat and detoxifying	Matrine, *etc.*	Hepatocarcinoma after TACE	122	Protect liver function	[81]
Jia Wei Si Jun Zi Tang and TACE	Tonifying spleen, nourishing Qi, soothing liver-Qi stagnation, and dissolving stasis	Dang-Shen (*Codonopsis pilosula*), Bai-Zhu (*Atractylodes macrocephala* Koidz.), Huang Qi (*Astragalus membranaceous*), Fo-Shou (*Citrus medica* L. var. *sarcodactylis*), Dan-shen (*Salvia miltiorrhiza* Bge.), *etc.*	Advance stage of liver cancer	65	Protect liver function	[82]

Vascular Embolizing Agent	Vascular embolizing	Yu-Jin (*Curcuma aromatic*), Bai-Ji (*Bletilla striata*)	Stage Ⅱ and Ⅲ hepatocarcinoma (Yu-Jin), stage Ⅰ-Ⅲ hepatocarcinoma (Bai-Ji)	32 (Yu-Jin), 106 (Bai-Ji), 56 (Bai-Ji)	Vascular embolizing agent	[83-85]
Aidi Injection and RFA or MWA	Dissipating mass, tonifying Qi and Yin	Ban-Mao (Mylabris), Huang Qi (*Astragalus membranaceous*), *etc.*	Middle-late stage hepatocarcinoma, stage Ⅱ and Ⅲ hepatocarcinoma	89, 61	Relieve the impairment of cool-tip radiofrequency ablation on hepatic function, improve immune function and reduce relapse; elevate MWA efficacy, improve QOL, immune and liver function	[86,92]
Xiaoaiping Injection and RFA	Dissolving stasis	Xiaoaiping injection	Middle-late stage hepatocarcinoma, advanced hepatocarcinoma	31, 68	Enhance RFA effects and reduce non-bacterial inflammatory response; inhibit tumor growth, improve QOL and immune function, increase progression-free survival	[87,99]
Tianzhicao Capsule and RFA	Detoxifying, dissolving stasis, tonifying Qi and Yin	Ban-Zi-Lian (*Sculellaria barbata*), Dan-shen (*Salvia miltiorrhiza* Bge.), Huang Qi (*Astragalus membranaceous*), Gou-Qi (*Lycium barbarum*), *etc.*	Small hepatocarcinoma	90	Improve QOL and immune function, prolong survival time	[88]
Fuzheng Yiliu Recipe and MWA		Huang Qi (*Astragalus membranaceous*), Ling-Zhi (*Ganoderma lucidum*), Nü-Zhen-Zi (*Ligustrum lucidum* Ait.), *etc.*	Middle-advanced stage hepatocarcinoma	60	Enhance MWA efficacy, improve immune and liver function	[90]
Shenqi Mixture and MWA	Tonifying Qi	Ren-Shen (*Panax ginseng*), *etc.*	Stage Ⅱ and Ⅲ hepatocarcinoma	72	Enhance MWA efficacy, prolong survival time, improve QOL and immune function and relieve symptoms	[91]
Qiankun Capsule and HIFU	Tonifying spleen, detoxifying, and dissipating mass	Tai-Zi-Shen (*Pseeudostellaria heterophylla*), Bai-Zhu (*Atractylodes macrocephala* Koidz.), Bai-Shao (*Paeonia lactiflora*), Xia-Ku-Cao (*Prunella*), Ban-Zi-Lian (*Sculellaria barbata*), *etc.*	Stage Ⅱ and Ⅲ hepatocarcinoma	60	Enhance therapeutic effects and improve immune function	[93]
Fu-Zhen-Yang-Yin Formula and HIFU	Tonifying Qi and Yin, detoxifying, and dissipating mass	Huang Qi (*Astragalus membranaceous*), Tai-Zi-Shen (*Pseeudostellaria heterophylla*), Yin-Chen-Hao (*Artemisia capillaris* Thunb.), Bai-Hua-She-She-Cao (*Hedyotis diffusa* Willd.), Hu-Zhang (*Polygonum cuspidatum*), *etc.*	Advanced stage hepatocarcinoma	60	Alleviate HIFU induced fever and liver function damage	[94]
Syndrome Differentiation Based TCM Therapy and Sorafenib	Syndrome differentiation based TCM therapy	Huang Qi (*Astragalus membranaceous*), Shan-Yao (*Dioscorea opposita*), Long-Kui (*Solanum nigrum* L.), Bai-Shao (*Paeonia lactiflora*), *etc.*	Advanced stage hepatocarcinoma	18	Enhance therapeutic efficacy of sorafenib and prolong survival time	[95]
Cinobufagin tablet and Sorafenib	Dissipating mass	Cinobufagin, *etc.*	Middle-advanced stage hepatocarcinoma	59	Enhance effects of sorafenib, improve QOL and liver function and relieve pain	[96]
Oleum fructus bruceas intervention, oral intake of Ganji Decoction and external application of Ailitong	Tonifying spleen, soothing liver-Qi stagnation, detoxifying, dissipating mass	Dang-Shen (*Codonopsis pilosula*), Chai-Hu (*Bupleurum scorzonerifolfium* Willd), Bai-Shao (*Paeonia lactiflora*), Tu-Bie-Chong (*Eupolyphaga gasinensis* Walk.), Bai-Hua-She-She-Cao (*Hedyotis diffusa* Willd.), *etc.*	Middle-advanced stage hepatocarcinoma	97	Prolong survival time, improve QOL and relieve pain	[97]

Hepatic artery perfusion/embolization with turmeric oil microballoon, cinobufotalin and Aidi injection, and Syndrome Differentiation Based TCM Therapy	Tonifying Qi and Yin, and dissipating mass	Yu-Jin (*Curcuma aromatic*), cinobufotalin, Ban-Mao (Mylabris), Huang Qi (*Astragalus membranaceous*), *etc.*	Stage Ⅰ to Ⅲ hepatocarcinoma	41	Inhibit tumor growth with fewer adverse reactions, and ameliorate fatigue and anorexia	[98]
Cinobufacini Injection	Dissipating masses	Cinobufagin, *etc.*	Middle-advanced stage hepatocarcinoma	100	Inhibiting tumor growth, protecting liver function and prolonging survival time	[100]
Norcantharidin and herbal decoction	Tonifying spleen and Qi, and dissolving stasis	Huang Qi (*Astragalus membranaceous*), Yin-Chen-Hao (*Artemisia capillaris* Thunb.), Hu-Zhang (*Polygonum cuspidatum*), Fu-Ling (*Poria cocos*), Tian-Long (Gecko), *etc.*	Elderly patients with late stage hepatocarcinoma	79	Inhibit tumor growth, prolong survival time and improve QOL	[101]
Jianpi Fuzheng Decoction	Tonifying Qi and Yin	Huang Qi (*Astragalus membranaceous*), Yi-Yi-Ren (*Coix lacryma-jobi* L.), Dang-Shen (*Codonopsis pilosula*), Bai-Zhu (*Atractylodes macrocephala* Koidz.), Nü-Zhen-Zi (*Ligustrum lucidum* Ait), *etc.*	Late stage hepatocarcinoma	60	Ameliorate TCM syndrome, improve QOL and immune function and prolong survival time	[102]
Jianpi Yiliu Decoction	Tonifying spleen and Qi, detoxifying, and dissolving stasis	Huang Qi (*Astragalus membranaceous*), Dang-Shen (*Codonopsis pilosula*), Bai-Zhu (*Atractylodes macrocephala* Koidz.), Ban-Zi-Lian (*Sculellaria barbata*), Yu-Jin (*Curcuma aromatic*), *etc.*	Late stage hepatocarcinoma	30	Ameliorate symptoms, improve QOL and protect liver function	[102]
Jiawei Yiguanjian	Tonifying Yin, clearing heat and draining dampness	Bei-Sha-Shen (*Glehnia littoralis*), Mai-Dong (*Ophiopogon japonicus*), Dang-Gui (*Angelica sinensis*), Gou-Qi (*Lycium barbarum*), Chui-Pen-Cao (*Sedum sarmentosum* Bunge), *etc.*	Late stage hepatocarcinoma	100	Prolong survival time, ameliorate TCM syndrome, and improve QOL and immune function	[104]

TCM: Traditional Chinese Medicine; TACE: Transarterial chemoembolization; RFA: Radiofrequency ablation; MWA: Microwave ablation; QOL: Quality of life; HIFU: High intensity focus ultrasound; HACE: Hepatic artery chemoembolization.

yiliu recipe after operation for 2 years are effective to prolong survival time and prevent recurrence in patients with stage Ⅲ hepatocarcinoma[74].

TCM in combination with TACE

TACE is the principle treatment for unresectable hepatocarcinoma. TCM has been used to improve efficacy of TACE. JDF granule preparation, a traditional Chinese herbal formula, combined with TACE may prolong survival time in patients with unresectable hepatocellular carcinoma[75]. Shentao Ruangan pill based herbal therapy in combination with TACE could prolong survival time in patients with middle-advanced stage liver cancer[76]. Ganai No. Ⅰ and No. Ⅱ in combination with hepatic artery chemoembolization (HACE) have been reported effectively to prolong survival time, prevent recurrence and alleviate HACE induced leukocytopenia in patients with middle-advanced stage hepatocarcinoma[77].

Jinlong Capsule may enhance short-term effect of TACE and improve QOL in patients with unresectable hepatocarcinoma[78]. Syndrome differentiation based TCM therapy could enhance short-term efficacy and reduce adverse effect of TACE, improve immune function and QOL in liver cancer patients[79]. Shelian Capsule, a Chinese patent drug, was reported to effectively enhance short-term efficacy of TACE, improve immune function and QOL in liver cancer patients[80]. Matrine injection and "jia wei si jun zi tang" have been proved effective to protect liver function in liver cancer patients receiving TACE treatment[81,82].

In addition to oral and intravenous administration, some Chinese herbs, such as *curcuma* aromatic and *Bletilla striata*, have been demonstrated to be able to be used as vascular embolizing agents for TACE in liver cancer patients[83-85].

TCM in combination with RFA

RFA is another widely used treatment for hepatocarcinoma. Aidi injection, an herbal injection, has been reported to effectively relieve hepatic function impairment caused by cool-tip RFA, improve immune function and reduce relapse rate in patients with liver cancer[86]. Xiaoaiping injection, an herbal extract injection, could enhance RFA effects and reduce non-bacterial inflammatory response post RFA[87]. Tianzhicao capsule in combination with RFA may improve QOL and immune function, prolong survival time in patients with hepatocellular carcinoma[88]. Jinlong capsule has been demonstrated to enhance RFA effects, reduce RFA induced liver injury, improve QOL and immune function in liver cancer patients[89].

TCM in combination with MWA

In combination with MWA, Fuzheng Yiliu Recipe could enhance MWA efficacy, improve immune and liver function in liver cancer patients[90]. Shenqi mixture has been showed to be effective to enhance MWA efficacy, prolong survival time, improve QOL and immune function and relieve symptoms in patients with hepatocarcinoma[91]. Aidi injection is able to elevate MWA efficacy and improve QOL, immune and liver function in hepatocarcinoma patients[92].

TCM in combination with other treatments

HIFU has become an important treatment method for hepatocarcinoma. In combination with HIFU, Qiankun capsule can enhance therapeutic effects and improve immune function in patients with hepatocarcinoma[93]. Fu-Zhen-Yang-Yin formula could alleviate HIFU induced fever and liver function damage[94].

Sorafenib is a target agent for liver cancer treatment. Syndrome differentiation based TCM therapy could enhance therapeutic efficacy of sorafenib and prolong survival time in patients with advanced hepatocarcinoma[95]. Cinobufagin tablet has been confirmed to enhance effects of sorafenib, improve QOL and liver function and relieve pain in liver cancer patients[96].

TCM as a monotherapy

In addition to intravenous administration, herbal extract injection also can be used as a perfusion/embolization reagent instead of chemotherapeutic drug. Tian *et al*[97] reported that a Chinese medicine comprehensive therapy, *i.e.,* Oleum fructus bruceas intervention combined with oral intake of Ganji Decoction and external application of Ailitong, is safe and effective to prolong survival time, improve QOL and relieve pain compared with conventional TACE in liver cancer patients[97]. Xu *et al*[98] has demonstrated that hepatic artery perfusion/embolization with turmeric oil microballoon, cinobufotalin and Aidi injection is effective with fewer adverse reactions compared with conventional TACE, and could significantly ameliorate fatigue and anorexia in patients with hepatocarcinoma[98].

Chinese patent herbal drugs have been approved as effective treatments for hepatocarcinoma. Xiaoaiping injection is effective to inhibit tumor growth, improve QOL and immune function, increase progression-free survival compared with best supportive treatment in patients with advanced hepatocarcinoma[99]. Cinobufacini injection has been demonstrated to be effective in inhibiting tumor growth, protecting liver function and prolonging survival time in patients with moderate and advanced hepatocarcinoma[100]. Norcantharidin in combination with herbal decoction treatment can inhibit tumor growth, prolong survival time and improve QOL in elderly patients with late stage liver cancer[101].

Herbal decoction is the principle TCM treatment for liver cancer. Jianpi Fuzheng decoction, an herbal formula for tonifying spleen and strengthening body defense, is effective in ameliorating TCM syndrome, improving QOL and immune function and prolonging survival time in patients with advanced liver cancer[102]. Jianpi Yiliu decoction, a formula for tonifying spleen and inhibiting tumor, has been reported to effectively ameliorate symptoms, improve QOL and protect liver function in patients with late stage hepatocarcinoma[103]. Jiawei Yiguanjian, a modified classical herbal formula, has been shown to be effective to prolong survival time, ameliorate TCM syndrome, and improve QOL and immune function in patients with advanced hepatocellular carcinoma[104].

EFFECTIVE MECHANISM OF CHINESE HERB AGAINST HEPATOCARCINOMA

The effects of Chinese herbs against hepatocarcinoma have been extensively studied, and it has been demonstrated that Chinese herbs are effective to induce apoptosis, autophagy, anoikis and cell senescence, arrest cell cycle, regulate immune function, inhibit metastasis and angiogenesis, reverse drug resistance and enhance effects of chemotherapy. Anti-cancer effects of herbal formulas against hepatocarcinoma are listed in Table 3.

Induction of apoptosis

Apoptosis is one of the most frequently studied filed for elucidating effective mechanism of herbs against hepatocarcinoma. Ren-Shen (*Panax ginseng*) is a commonly used Qi-tonifying herb. 20(R)-ginsenoside Rg3, a component from *Panax ginseng*, may up-regulate TNF-α and induce apoptosis in induced liver tumors in SD rats[105]. Blood tonifying herb or component, including Di-Huang (*Rehmannia glutinosa*) and N-butylidenephthalide from Dang-Gui (*Angelica sinensis*), is effective to induce apoptosis of hepatocarcinoma cells[106,107]. Gou-Qi (*Lycium barbarum*), a liver-Yin tonifying herb, is effective to inhibit proliferation and stimulate p53-mediated apoptosis in liver cancer cells[106]. Icariin, an ingredient from Yang tonifying herb Yin-Yang-Huo (*Epimedium brevicornum* Maxim.), may generate reactive oxygen species (ROS) and up-regulate JNK (c-Jun N-terminal kinase) phosphorylation and B-cell lymphoma 2/Bcl2-associated

Table 3 Anti-cancer effects of herbal formulas against hepatocarcinoma

Herbal formula	Therapeutic principles	Herbs	Models	Effects	Targets/events	Ref.
Fuzheng Yiliu Granule	Tonifying Qi and blood, and dissolving stasis	Hong-Qi (*Hedysarum polybotrys*), Dang-Gui (*Angelica sinensis*), Mu-Tou-Hui (*Patrinia scabra* Bunge), *etc.*	Mouse H22 hepatocarcinoma bearing mice	Inhibit tumor growth, induce apoptosis	p53, caspase-3, mitochondrial membrane potential	[126,127]
Fuganchun 6	Tonifying Qi and Yin, detoxifying and dissipating mass	Huang-Qi (*Astragalus membranaceus*), Nü-Zhen-Zi (*Ligustrum lucidum* Ait), Bai-Hua-She-She-Cao (*Hedyotis diffusa* Willd), Bie-Jia (Carapax trionycis), E-Zhu (*Curcuma kwangsiensis* or *Curcuma phaeocaulis* or *Curcuma wenyujin*), *etc.*	Mouse H22 hepatocarcinoma cells *in vitro* and *in vivo*	Inhibite tumor growth and cell proliferation, and induce apoptosis	Enhance proliferation activity of lymphocyte, NK cells activities and IL-2 production	[128,178]
Bushen Jianpi Decoction	Tonifying spleen and kidney	Dang-Shen (Codonopsis pilosula), Bai-Zhu (*Atractylodes macrocephala* Koidz.), Fu-Ling (Poria cocos), Shu-Di-Huang (*Rehmannia glutinosa*), shan-Zhu-Yu (*Cornus officinalis*), Du-Zhong (*Eucommia ulmoides* Oliver), *etc.*	Mouse H22 hepatocarcinoma bearing mice	Inhibit tumor growth, induce apoptosis	VEGF	[129]
Warming Yang and Dispersing Stasis Formula	Warming Yang and dispersing stasis	Fu-Zi (*Aconitum carmichaeli* Debx.), Huang-Qi (*Astragalus membranaceus*), Bai-Zhu (*Atractylodes macrocephala* Koidz.), E-Zhu (*Curcuma kwangsiensis* or *Curcuma phaeocaulis* or *Curcuma wenyujin*), Bai-Shao (*Paeonia lactiflora*), *etc.*	Human BEL-7402 hepatocarcinoma cells	Induce apoptosis	Unknown	[130]
Fufangkushen injection	Clearing heat and removing toxicity	Ku-Shen (*Sophora flavescens* Ait.), *etc.*	Human SMMC-7721 hepatocarcinoma cells	Inhibit proliferation, induce apoptosis	Survivin, Bcl-2, caspase-3	[131]
Songyou Yin	Tonifying Qi and blood, dissolving stasis and dissipating mass	Dan-shen (*Salvia miltiorrhiza* Bge.), Huang-Qi (*Astragalus membranaceus* Bge.), Gou-Qi (*Lycium barbarum* L.), Shan-Zha (*Crataegus pinnatifida* Bge.), and Bie-Jia (*Trionyx sinensis* Wiegmann)	Human MHCC97H hepatocarcinoma bearing nude mice; activated rat hepatic stellate cells and rat McA-RH7777 hepatoma cells	Induce apoptosis, inhibit tumor growth, prolong survival; inhibit invasion and metastasis	MMP-2, IL-6, TGF-β1, VEGF, epithelial-mesenchymal transition	[132,167]
Huang-lian-jie-du-tang	Clearing heat and removing toxicity	Huang-Lian (*C. chinensis* Franch), Huang-Qin (*Scutellaria baicalensis* Georgi), Huang-Bai (*P. amurense* Rupr) and Zhi-Zi (*Gardenia jasminoides* Ellis)	Human Hep G2 and PLC/PRF/5 hepatomain cells *in vitro* and *in vivo*	Inhibit cell proliferation, induce cell cycle arrest and apoptosis	Cdc2, Cdc25C, cyclin A, cyclin B1, Cdc2, Cdc25C, Bax, Bak, Bcl-2, Bcl-XL, IkappaBalpha	[141]
Bu-Zhong-Yi-Qi-Tang	Invigorating spleen-stomach and replenishing qi	Huang-QI (*Astragalus membranaceus*), Ren-Shen (*Panax ginseng*), Gang-Gui (*Angelicae sinensis*), Sheng-Ma (*Cimicifuga foetida* L.), Gan-Cao (*Glycyrrhiza uralensis*), Chen-Pi (*Citrus poonensis*), Chai-Hu (*Bupleurum chinensis*), Sheng-Jiang (*Zingiber officinale*), Da-zhao (*Ziziphs jujuba*), Bai-Shu (*Atractylodes macrocephala* KOIDZUMI)	Human hepatoma Hep3B, HepG2 and HA22T cells	Inhibit cell proliferation, induce apoptosis and arrest cell cycle at G0/G1 phase	Unknown	[142]
Jiedu Xiaozheng Yin	Heat-clearing and detoxification	Bai-Hua-She-She-Cao (*Hedyotis diffusa* Willd), Xia-Ku-Cao (*Prunella*), Shan-Ci-Gu (*Pseudobulbus Cremastrae*), Ku-Shen (*Sophora flavescens*)	Human Hep G2 hepatoma cell *in vitro* and *in vivo*	Inhibits the growth of HepG2 cells, arrest cell cycle at the G0/G1 phase	Cyclin D and cyclin E	[143]
Liver Yin Tonifying formula	Tonifying liver-Yin, draining dampness and dissipating stasis	Nü-Zhen-Zi (*Ligustrum lucidum* Ait), Zhi-Bie-Jia (processed Carapax trionycis) and Hu-Zhang (*Polygonum cuspidatum*)	Human hepatocarcinoma Bel-7402 cells	Inhibit proliferation, induce apoptosis and cell senescence	Caspases-8, -9 and -3, p16, p21, pRB	[152]
Modified Yi Guan Jian	Tonifying liver and kidney-Yin, draining dampness and dissipating stasis	Bei-Sha-Shen (*Glehnia littoralis*), Mai-Dong (*Ophiopogon japonicus*), Dang-Gui (*Angelica sinensis*), Shu-Di (dried *Rehmannia glutinosa*), Gou-Qi (*Lycium barbarum*), Chuan-Lian-Zi (*Melia toosendan* Sieb fruit), and Hu-Zhang (*Polygonum cuspidatum*)	Human hepatocarcinoma Bel-7402 cells	Inhibit proliferation, induce anoikis	Caspases-3, -8 and -9, p38 MAPK	[156]
Blejiajian Pill	Tonifying Qi, detoxifying and dissipating mass	Bie-Jia-Jiao(Carapacis trionycis-shell glue), E-Jiao(Colla Corii Asini), Feng-Fang (beehives), Chai-Hu (*Bupleurum chinense*), Huang-Qin (*Scutellaria baicalensis*), Ban-Xia (*Pinellia ternate*), Dang-Shen(*Codonopsis pilosula*), *etc.*	Human Hep G2 hepatoma cells	Inhibit cell proliferation, adhesion and invasion	Unknown	[168]

Compound Astragalus and Salvia miltiorrhiza extract	Tonifying Qi and dissipating stasis	Astragalosides, astragalus polysaccharide and salvianolic acids	Human Hep G2 hepatoma cells	Inhibit TGF-β1 mediated invasion	TGF-β/Smad signaling	[169]
Shehuang Xiaoliu Fang	Tonifying spleen, dissolving stasis and detoxifying	She-Xiang (musk), Niu-Huang (Cow-Bezoar), Dan-shen (*Salvia miltiorrhiza* Bge.), Bai-Zhu (*Atractylodes macrocephala* Koidz.), Ban-Zi-Lian (*Sculellaria barbata*), E-Zhu (*Curcuma kwangsiensis* or *Curcuma phaeocaulis* or *Curcuma wenyujin*), *etc.*	Human SMMC-7721 hepatocarcinoma cells	Inhibit invasive and adhesive	nm23-h1 and ICAM-1	[170]
Xiaochaihu Decoction	Relief liver for smooth Qi	Chai-Hu (*Bupleurum chinense*), Huang-Qin (*Scutellaria baicalensis* Georgi), Sheng-Jiang (*Zingiber officinale*), Ban-Xia (*Pinellia ternata*), Da-Zao (*Ziziphus jujuba*), Ren-Shen (*Panax ginseng*), Gan-cao (*Glycyrrhiza uralensis*)	Mouse H22 hepatocarcinoma bearing mice	Inhibit tumor growth	Increase T lymphocytes proliferation, NK cells activities and IL-2	[175]
Mylabris Mixture	Detoxifying and dissipating mass	Ban-Mao (Mylabris), Chen-Pi (*Citrus reticulata* Blanco), Gu-Ya (Setaria italica), *etc.*	Mouse H22 hepatocarcinoma bearing mice	Inhibit tumor growth	Increase $CD4^+$, $CD8^+$ lymphocytes and NK cells, and IFN-γ and IL-4 production	[176]
Fuzheng Yiliu Granule-2	Tonifying Qi and tonifying Yin	Huang-Qi (*Astragalus membranaceus*), Nü-Zhen-Zi (*Ligustrum lucidum* Ait), Ling-Zhi (*Ganoderma lucidum*), and Shan-Yao (*Dioscorea opposita*)	Mouse H22 hepatocarcinoma cells *in vitro* and *in vivo*	Inhibite tumor growth and cell proliferation, and induce apoptosis	Increase $CD4^+$ lymphocyte, IL-2 and TNF-α, and NK cells	[177]
Fu-Zheng-Kang-Ai-Tang	Strengthening body resistance and anti-cancer	Ren-Shen (Panax ginseng), Huang-Qin (*Scutellaria baicalensis* Georgi), Ling-Zhi (*Ganoderma lucidum*), Huang-Qi (*Astragalus membranaceus*), *etc.*	Human Bel-7402 hepatocarcinoma bearing nude mice	Inhibit angiogenesis and tumor growth	VEGF and bFGF	[188]
Delisheng	Tonifying Qi and resolving masses	Ren-Shen (Panax ginseng), Huang-Qi (Astragalus membranaceus), Cantharidium, *etc.*	Human Hep G2 hepatoma cells	Inhibit tumor growth	Endostatin	[189]
QHF	Detoxifying, dissolving stasis and strengthening body resistance	Cinobufagin, Ginsenoside Rg3, Panax Notoginseng Saponins, lentinan	Mouse H22 hepatocarcinoma bearing mice	Inhibit angiogenesis and tumor growth, enhance anti-cancer effects DDP	VEGF, EGFR and MMP-2	[190,196]
Erbie San	Resolving masses	Bie-Jia (Carapax trionycis), *etc.*	Wistar rats bearing Walker-256 liver cancer	Inhibit tumor growth	VEGF and endostatin	[191]
Chaiqiyigan Granula	Tonifying spleen, soothing liver, dissolving stasis and detoxifying	Chai-Hu (*Bupleurum chinense*), Huang-Qi (*Astragalus membranaceus*), *etc.*	Human hepG2/EGFP hepatoma bearing nude mice	Enhance anti-cancer effects of Taxol	Bax, p53 and VEGF	[195]
Shengmai Injection	Tonifying Qi and Yin	Ren-Shen (*Panax ginseng*), Mai-Dong (*Ophiopogon japonicus*), *etc.*	Mouse H22 hepatocarcinoma bearing mice	Enhance anti-tumor efficacy and reduce toxicity of 5-Fu	Unknown	[197]

TGF: Transforming growth factor; IL-2: Interleukin-2; ICAM-1: Intercellular adhesion molecule 1; TNF: Tumor necrosis factor; VEGF: Vascular endothelial growth factor; MMP2: Matrix metalloproteinase-2; bFGF: Basic fibroblast growth factor; NK: Natural killer; IFN-γ: Interferon-γ; MAPK: Mitogen-activated protein kinases; Bcl-2: Bcl2-associated X protein; Cdc25B: Cell division cycle 25B.

X protein (Bax/Bcl-2) to induce intrinsic apoptosis in liver cancer cells[108].

Clearing heat and detoxifying herbs are one of the most commonly medicated herbs for liver cancer treatment. Solamargine purified from Long-Kui (*Solanum incanum*) may up-regulate TNF receptor type Ⅰ and induce apoptosis in Hep3B cells[109]. Components from Mao-Ren-Shen (*Actinidia valvata*) may arrested cell cycle at G0/G1 phase and induce apoptosis in H22 cells[110]. Ban-Zi-Lian (*Scutellariae barbata*) is effective in up-regulating Bax/Bcl-2, arresting cell cycle at G2/M phase and inducing apoptosis in hepatocellular carcinoma cells[111]. Ba-Qia (*Smilax glabra* Roxb.) extract could activate p38, JNK and extracellular signal-regulated kinase (ERK) to induce intrinsic apoptosis in liver cancer cells[112]. Essential oil of Qing-Hao (*Artemisia annul* L.) could induce apoptosis in SMMC-7721 cells[113].

Clearing heat and draining dampness herbs are used for damp-heat in the liver and gallbladder. Chui-Pen-Cao (*Sedum sarmentosum* Bunge) can inhibit HepG2 cell

growth and induce apoptosis accompanied by down-regulation of Bcl-2, VEGF and phosphorylated signal transducers and activators of transcription (p-STAT3)[114]. Resveratrol-4-O-D-(2'-galloyl)-glucopyranoside from Hu-Zhang (*Polygonum cuspidatum*) may activate caspases 3 and 9 to induce apoptosis in hepatocellular carcinoma *via* the JNK and ERK pathway[115]. Yin-Chen-Hao (*Artemisia capillaris* Thunb.) is effective to induce apoptosis and G0/G1 cell cycle arrest in SMMC-7721 cells[116].

Dispersing blood stasis is another important principle for liver cancer therapy. Dan-Shen (*Salvia miltiorrhiza*) was reported to effectively inhibit proliferation and induce apoptosis in HepG2 cells coincided with depletion of intracellular glutathione and reduction of mitochondrial membrane potential[117]. Chi-Shao (*Paeoniae Radix*) could inhibit cell growth and induce p53 independent apoptosis coincided with up-regulation Bcl-2/adenovirus E1B 19 kD-interacting protein 3 and down-regulation of ZK1, RAD23 homologue B and heat shock 60 kDa protein 1[118]. Curcumin is a component of Yu-Jin/Jiang-Huang/E-Zhu (*Curcuma kwangsiensis* or *Curcuma phaeocaulis* or *Curcuma wenyujin* or *Curcuma longa*). Resveratrol is a compound that can be isolated from Hu-Zhang (*Polygonum cuspidatum*) or other plants. We have found that curcumin combined with resveratrol may synergistically inhibit X-linked inhibitor of apoptosis protein (XIAP) and survivin expression, up-regulate ROS production, activate caspases-3, -8 and -9 to induce apoptosis in liver cancer cells[119].

Although the TCM pathological factor of phlegm is not directly related to hepatocarcinogenesis, reducing phlegm and/or resolving masses herbs are frequently medicated as anti-cancer herbs in liver cancer. Ban-Xia (*Pinellia ternate*) can inhibit cell proliferation, up-regulate Bax/Bcl-2 and induce apoptosis in Bel-7402 cells[120]. Tian-Nan-Xing (*Arisaema heterophyllum*) may activate caspase-3 and induce apoptosis in hepatocarcinoma cells[121]. Tubeimoside Ⅰ, an ingredient from Tu-Bei-Mu (*Bolbostemma paniculatum*), could up-regulate Bax/Bcl-2 and induce intrinsic apoptosis in hepatoma cells[122]. Toxic Chinese herb or components such as Quan-Xie (scorpio), Norcantharidin and polypeptides from bee venom are potent to induce apoptosis in liver cancer cells[123-125].

Contemporary TCM physicians have developed some new herbal formulas for liver cancer treatment. Fuzheng yiliu granule, a four herb formula for tonifying Qi and blood, and dissolving stasis, is effective to up-regulate p53 and caspase-3 expression and reduce mitochondrial membrane potential to induce apoptosis in H22 hepatocarcinoma[126,127]. Fuganchun 6, a formula for nourishing Qi and Yin, detoxifying and dissipating mass, could induce apoptosis and arrest cell cycle at G0/G1 phase[128]. Bushen jianpi decoction, a formula for tonifying kidney and spleen, was reported to inhibit VEGF expression and induce apoptosis in H22 hepatocarcinoma[129]. Warming yang and dispersing stasis formula may induce apoptosis in hepatocarcinoma Bel-7402 cells[130]. Fufangkushen injection, a patent herbal drug, may inhibit survivin and Bcl-2 expression, increase caspase-3 expression and induce apoptosis in SMMC-7721 cells[131]. Songyou Yin, another patent herbal drug, could induce apoptosis and down-regulation of MMP2 and VEGF to inhibit tumor growth and prolong survival[132] (Figure 1).

Arresting cell cycle

Sustaining proliferative signaling is a hallmark of cancer[133]. Cancer cells present an un-controlled proliferation cycle. To stop cell cycle is an ideal principle for cancer treatment. Some herbs are demonstrated to be potent to arrest cell cycle. Among tonic herbs, extracts of Jiao-Gu-Lan (*Gynostemma pentaphyllum*) can inhibit proliferation and arrest cell cycle at G0/G1 phase in Hep3B cells[134,135]. Triterpene-enriched extracts from Ling-Zhi (*Ganoderma lucidum*) could suppress protein kinase C, activate JNK and p38 mitogen-activated protein kinases (MAPK) to prolong G2 cell cycle phase and inhibit cell growth in Huh-7 cells[136].

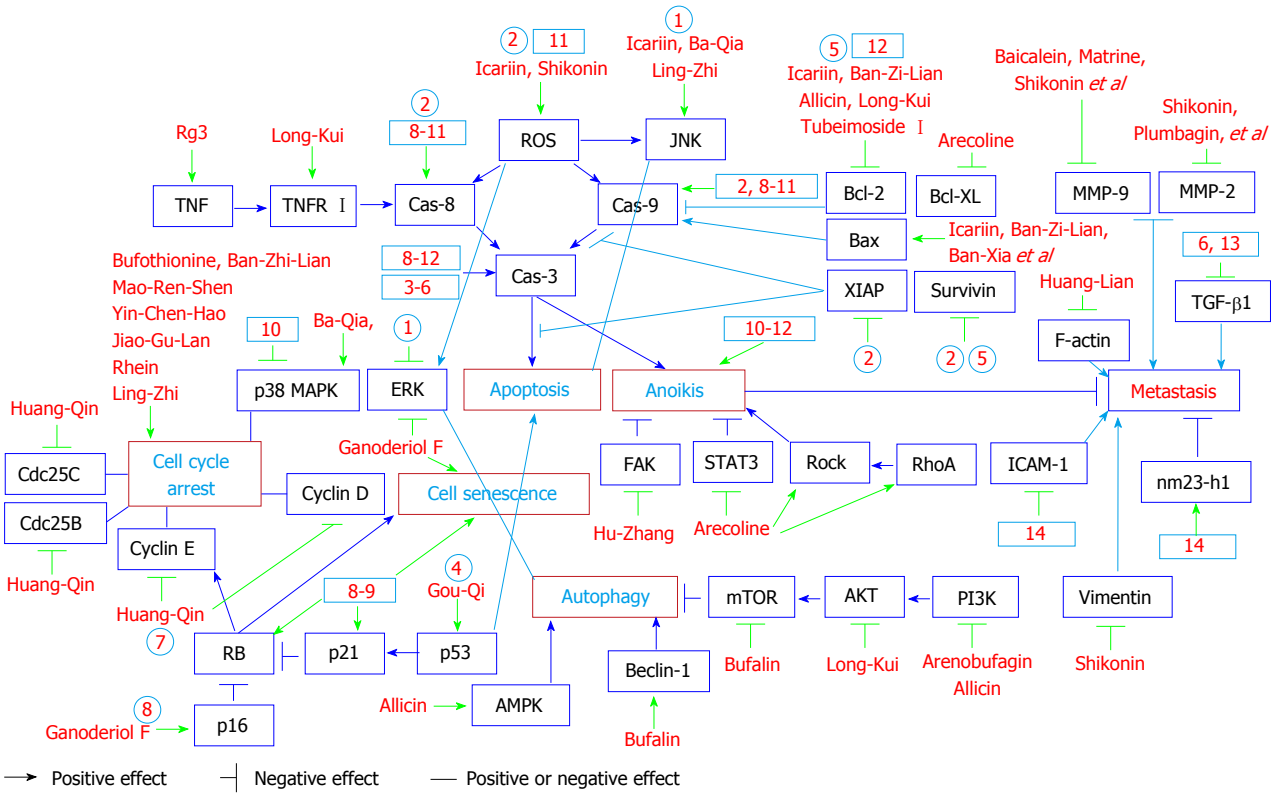
Ban-Zhi-Lian (*Scutellaria barbata*) is able to inhibit cell proliferation, decrease the number of cells in S-phase and increase the number of cells in G0/G1-phase and induce apoptosis in HepG2 cells [137]. Huang-Qin (*Scutellaria baicalensis*) is effective to inhibit cell growth and G2/M phase arrest accompanied by increased Cyclin E and down-regulation of p53, ETS1 (V-ets avian erythroblastosis virus E26 oncogene homolog 1), cell division cycle 25B (Cdc25B), p63, epidermal growth factor receptor (EGFR), ERK1/2, XIAP, HIF-2alpha, and Cdc25C[138]. Bufothionine also can inhibit cell proliferation and arrest cell cycle at G2/M phase in liver cancer cells[139]. Rhein, a component from Da-Huang (*Rheum palmatum* L. or *Rheum tanguticum* Maxim. ex Balf.), is potent to inhibit cell growth, induce apoptosis and arrest cell cycle at S phase[140].

Huang-lian-jie-du-tang, a classic herbal formula for clearing heat and removing toxicity, was reported to effectively inhibit cell proliferation, induce cell cycle arrest and apoptosis in hepatocarcinoma *in vitro* and *in vivo*[141]. Bu-Zhong-Yi-Qi-Tang, a Qi tonifying herbal formula, is confirmed effective to inhibit cell proliferation, induce apoptosis and arrest cell cycle at G0/G1 phase[142]. Jiedu Xiaozheng Yin, a modern herbal formula, could inhibit the growth of HepG2 cells and arrest cell cycle at the G0/G1 phase coincidence with up-regulation of cyclin D and cyclin E[143] (Figure 1).

Induction of autophagy

Autophagy, type Ⅱ programmed cell death, is a process in which organelles and proteins are sequestered and subsequently degraded through fusion with lysosomes, and has been recognized as a target for hepatocarcinoma treatment[144,145]. Long-Kui (*Solanum nigrum* L.), a frequently used anti-cancer herb, may induce apoptosis and down-regulate Bcl-2 and AKT to induce autophagy in hepatocarcinoma cells[146].

Arenobufagin, a natural bufadienolide from toad



1: Resveratrol-4-O-D-(2'-galloyl)-glucopyranoside; 2: Curcumin and resveratrol; 3: Tian-Nan-Xing (*Arisaema heterophyllum*); 4: Fuzheng yiliu granule; 5: Fufangkushen injection; 6: Songyou Yin; 7: Jiedu Xiaozheng Yin; 8: Liver-Yin tonifying formula; 9: Nü-zhen-zi (*Ligustrum lucidum* Ait. Fruit); 10: Modified Yi Guan Jian; 11: Hu-Zhang (*Polygonum cuspidatum*); 12: Arecoline; 13: Compound Astragalus and Salvia miltiorrhiza extract; 14: Shehuang Xiaoliu Fang.

Figure 1 Therapeutic targets of Chinese herb(s) in hepatocarcinoma cells. TNF: Tumor necrosis factor; ROS: Reactive oxygen species; JNK: C-Jun N-terminal kinase; Bax/Bcl-2: B-cell lymphoma 2/Bcl2-associated X protein; XIAP: X-linked inhibitor of apoptosis protein; MMP-2: Matrix metalloproteinase-2; TGF-β: Transforming growth factor-β; ICAM-1: Intercellular adhesion molecule 1; mTOR: Mechanistic target of rapamycin; AMPK: AMP-activated protein kinase; Cdc25B: Cell division cycle 25B; TNFR Ⅰ: Tumor necrosis factor receptor type Ⅰ; ERK: Extracellular signal-regulated kinase; FAK: Focal adhesion kinase; PI3K/Akt: Phosphatidylinositol-4,5-bisphosphate 3-kinaseV-akt murine thymoma viral oncogene homolog; STAT3: Signal transducers and activators of transcription 3.

venom, is potent to induce apoptosis and autophagy by down-regulation of PI3K/AKT/mechanistic target of rapamycin (mTOR) pathway in HepG2/ADM hepatoma cells, and thus inhibit xenograft tumor growth[147]. Bufalin, a component from toad skin, has been demonstrated to induce AMP-activated protein kinase (AMPK) dependent autophagy accompanied by enhanced Beclin-1 expression and LC3-Ⅰ to LC3-Ⅱ conversion, and decreased p62 expression and mTOR signaling in HepG2 cells[148].

Allicin, a major phytochemical of crushed garlic, is effective to induce autophagy in HepG2 cells by decreasing the level of cytoplasmic p53, the PI3K/mTOR signaling pathway, and Bcl-2 and up-regulating the expression of AMPK/tuberous sclerosis protein 2 and Beclin-1[149]. Shikonin, a naphthoquinone from Zi-Cao (*Lithospermum erythrorhizon*), could induce autophagy and reactive oxygen species generation which further activates ERK[150] (Figure 1).

Induction of cell senescence

Cell senescence is a state of stable, irreversible cell cycle arrest provoked by a variety of stimuli. Pro-senescence has been suggested for hepatocellular carcinoma treatment[151]. We have established a liver-Yin tonifying formula (LYTF) for liver-Yin-deficiency in patients with hepatocarcinoma. LYTF could activate caspases-8, -9 and -3 to induce apoptosis, and up-regulate p16 and p21 and down-regulate RB phosphorylation to induce cell senescence in Bel-7402 cells[152]. Ganoderiol F, a tetracyclic triterpene from *Ganoderma* amboinense, may activate ERK and up-regulate p16 to induce cell senescence in hepatoma HepG2 cells[153]. Nü-zhen-zi (*Ligustrum lucidum* Ait. Fruit), an herb for tonifying liver-Yin, is potent to up-regulate p21, activate caspases-8, -9 and -3 to induce apoptosis and down-regulate RB phosphorylation to induce cell senescence in hepatocarcinoma cells[154] (Figure 1).

Induction of anoikis

Anoikis, an apoptotic process occurring when cells detach from the extracellular matrix, is associated with metastasis of hepatocarcinoma[155,156]. We have found modified Yi Guan Jian, an herbal formula for hepatocarcinoma, may activate caspase-3, -8 and -9, inhibit the expression and phosphorylation of p38 MAPK, and induce anoikis in human hepatocarcinoma Bel-7402 cells[156]. Hu-Zhang (*Polygonum cuspidatum*), an herb for draining dampness and dissipating stasis, could activate caspase-3 and -9 and induce anoikis in

human hepatocarcinoma Bel-7402 cells accompanied by ROS generation and focal adhesion kinase down-regulation[157]. Arecoline, an alkaloid from Bing-Lang (*Areca catechu* L.), may induce anoikis in HA22T/VGH cells involving inhibition of STAT3 and increased RhoA/Rock (Ras homolog family member A/Rho-associated, coiled-coil containing protein kinase) activation[158] (Figure 1).

Inhibition of metastasis

In addition to induction of anoikis, Chinese herbs also could inhibit metastasis potential in hepatocarcinoma cells, such as adhesion, migration, invasion and metastasis. Among heat-clearing herbs, *Coptidis* Rhizoma (Huang-Lian) may reduce F-actin polymerization and damage to cytoskeleton network to inhibit hepatocarcinoma cell migration[159]. Baicalein, a compound from *Scutellaria baicalensis* Georgi (Huang-Qin), could inhibit migration and invasion in human hepatocellular carcinoma SMMC-7721 cells accompanied by down-regulation of ezrin, VEGF, and MMP-9[160]. Matrine, a component of *Sophora flavescens* Ait. (Ku-Shen), was reported to be effective to inhibit MMP-9 and nuclear factor κB (NF-κB) to inhibit invasion of liver cancer cells[161]. Shikonin, an ingredient of *Lithospermum erythrorhizon* (Zi-Cao), is potent to inhibit the migratory ability of hepatocarcinoma cells through downregulation of vimentin, MMP-2 and MMP-9[162].

Another frequently studied herbal type is dissolving stasis herbs. Gekko sulfated polysaccharide-protein complex has been demonstrated to be effective in inhibiting hepatocellular carcinoma cell migration through calcium-mediated regulation of the actin cytoskeleton reorganization[163]. Ardipusilloside, a compound from *Ardisia japonica* (Thunb) Blume (Zi-Jin-Niu), has the potential to inhibit liver cancer survival, invasion and metastasis by down-regulation of MMP-9 and MMP-2 and activating Ras-related C3 botulinum toxin substrate 1 (Rac 1) to enhance E-cadherin activity[164]. Plumbagin, a constituent of Plumbago zeylanica L. (Bai-Hua-Dan), could suppress the proliferation and invasiveness in SK-hep-1 cells by up-regulation of p21 and down-regulation of MMP-2 and MMP-9[165]. Tanshinone Ⅱ-A, a component from Dan-Shen (*Salvia miltiorrhiza*), could effectively inhibit invasion and metastasis of hepatocaxrcinoma cells partly by inhibiting MMP-2 and MMP-9 activities and blocking NF-κB activation[166].

Some herbal formulas have been confirmed to be effective against hepatocarcinoma metastasis. In addition to inhibiting liver cancer growth, Songyou Yin also could down-regulate activated hepatic stellate cells secreted IL-6, TGF-β1 and VEGF to reduce MMP-2 expression and reverse epithelial-mesenchymal transition, and thus inhibit invasion and metastasis in hepatocarcinoma[167]. Biejiajian pill, a classical herbal formula, could effectively inhibit HepG2 cell proliferation, adhesion and invasion[168]. Compound *Astragalus* and *Salvia miltiorrhiza* extract, an herbal component formula made up of astragalosides, astragalus polysaccharide and salvianolic acids, may inhibit TGF-β1 mediated invasion in HepG2 hepatoma cells through modulating TGF-beta/Smad signaling[169]. Shehuang Xiaoliu Fang, an herbal formula for detoxifying and dissipating masses, is potent to inhibit invasive and adhesive ability of SMMC-7721 cells accompanied by increased nm23-h1 expression and reduced ICAM-1 expression[170] (Figure 1).

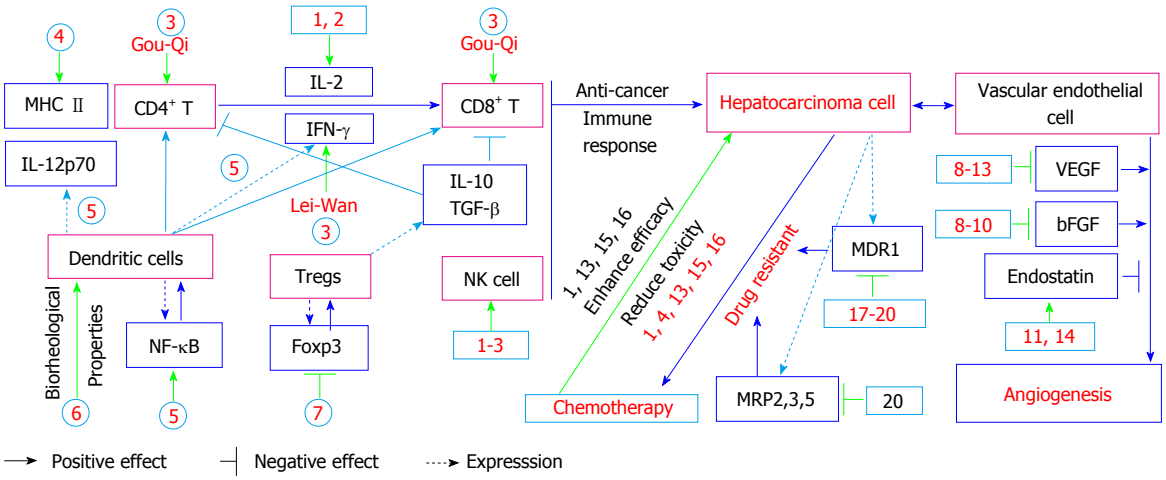
Regulation of immune function

$CD4^+$ and $CD8^+$ T lymphocytes are the major cell populations for cellular immunity against cancer. *Lycium barbarum* (Gou-Qi) polysaccharides could increase $CD4^+$ and $CD8^+$ T cells in tumor-infiltrating lymphocytes in H22 hepatoma[171]. Dong-Chong-Xia-Cao (*Cordyceps sinensis*), a commonly used herb for tonifying kidney, may increase the expression of major histocompatibility complex class Ⅱ antigens on human hepatoma HA22T/VGH cells[172]. Ban-Zi-Lian (*Scutellaria barbata*), an effective anti-cancer herb for hepatocarcinoma, could increase the thymus and spleen index, lymphocytes proliferation activities, natural killer (NK) cell activities and IL-2 production in splenocytes[173]. The proteins extracted from mycelia of Lei-Wan (*Omphalia lapidesces*) are effective in increasing spleen mass and interferon-γ (IFN-γ) production in H22 hepatocarcinoma bearing mice[174].

Xiaochaihu decoction, a classical herbal formula for liver disease, is effective in inhibiting tumor growth and increasing T lymphocyte proliferation, NK cells activities and IL-2 level in H22 bearing mice[175]. Mylabris Mixture, a modern anti-hepatoma herbal formula, may increase $CD4^+$, $CD8^+$ lymphocytes and NK cells, and IFN-γ and IL-4 production in H22 cancer-bearing mice[176]. Fuzheng Yiliu Granule, an effective pro-apoptosis contemporary herbal formula, may increase $CD4^+$ lymphocytes and related cytokines IL-2 and TNF-α, and NK cells in H22 tumor-bearing mice[177]. Fuganchun 6, a modern herbal formula, can inhibit tumor growth and enhance proliferation activity of lymphocytes, NK cell activities and IL-2 production in H22 hepatoma bearing mice[178].

Dendritic cells (DCs) are important antigen present cells for anti-cancer immunity. *Lycium barbarum* (Gou-Qi) polysaccharides could promote DCs to stimulate allogeneic lymphocyte proliferation, produce IL-12p70 and IFN-γ and may relate to NF-κB expression[179]. Chen *et al*[180] found that human hepatocellular carcinoma SMMC-7721 cells may impair the biorheological properties of DCs, such as cell deformability, migration, and electrophoresis mobility, and changed organizations of cytoskeletal proteins. Gekko (Tian-Long) sulfated polysaccharide-protein complex could partially restore the defective biorheological characteristics of DCs mediated by SMMC-7721 cells[180].

$CD4^+$ $CD25^+$ regulatory T cells (Tregs) are originated from $CD4^+$ Th0 cells upon the stimulation of TGF-β and Foxp3 expression. Tregs may produce IL-10 and function as a negative immune regulator. *Radix Glycyrrhizae* (Gan-Cao) polysaccharides were demonstrated to down-regulate Tregs, related cytokines IL-10 and TGF-β,



1: Ban-Zi-Lian (*Sculellaria barbata*); 2: Xiaochaihu decoction; 3: Mylabris Mixture; 4: Dong-Chong-Xia-Cao (*Cordyceps sinensis*); 5: Gou-Qi (*Lycium barbarum*) polysaccharide; 6: Gekko (Tian-Long) sulfated polysaccharide-protein complex; 7: *Radix Glycyrrhizae* (Gan-Cao) polysaccharide; 8: Tian-Long (Gekko Chinenis); 9: Gekko-sulfated glycopeptide; 10: Fu-Zheng-Kang-Ai-Tang; 11: Erbie San; 12: Huaier; 13: QHF; 14: Delisheng; 15: Chaiqiyigan granula; 16: Shengmai Injection; 17: *Astragalus* polysaccharides; 18: Astragaloside Ⅱ; 19: Green tea catechins; 20: Tetramethylpyrazine.

Figure 2 Therapeutic targets of Chinese herb(s) in regulating immune function, inhibiting angiogenesis and combinational treatment with chemotherapy in hepatocarcinoma. TGF-β: Transforming growth factor-β; IFN-γ: Interferon γ; IL-6: Interleukin 6; VEGF: Vascular endothelial growth factor; bFGF: Basic fibroblast growth factor; MRP2: Multi-drug resistance protein 2; NF-κB: Nuclear factor-κB; NK: Natural killer.

and Foxp3 expression, and increased IL-2 and IL-12p70 levels in serum in H22 hepatocarcinoma bearing mice[181] (Figure 2).

Inhibition of angiogenesis

Angiogenesis, the process of new blood vessel generation from existing vessels, plays a crucial role in tumor growth and metastasis, and has been suggested as a potential target for hepatocarcinoma prevention and treatment[182,183].

Tian-Long (Gekko Chinenis) has been showed to be effective to inhibit tumor growth, induce apoptosis, and inhibit angiogenesis accompanied by down-regulation of VEGF and basic fibroblast growth factor (bFGF) in H22 hepatocarcinoma[184]. Gekko-sulfated glycopeptide may inhibit angiogenesis by decreasing bFGF secretion, and binding to heparin/heparan sulfate in liver cancer[185]. Bai-Ji (*Bletilla* colloid) could inhibit endothelial cell growth and angiogenesis after TACE[186]. Huaier may inhibit VEGF expression and angiogenesis, induce apoptosis and inhibit tumor growth in hepatocarcinoma[187].

Fu-Zheng-Kang-Ai-Tang, an herbal formula for strengthening body defense and anti-cancer, could inhibit VEGF and bFGF expression, angiogenesis and tumor growth in hepatocarcinoma[188]. Delisheng, an herbal formula for tonifying Qi and resolving masses, may inhibit cell growth and increase endostatin expression in hepatocellular carcinoma HepG2 cells[189]. Qingrejiedu, huoxuehuayu and fuzhengguben (QHF) formula, an herbal component formula, is potent to inhibit VEGF, EGFR and MMP-2, angiogenesis and tumor growth[190]. Erbie San, a patent herbal drug for resolving masses, was demonstrated to be effective to down-regulate VEGF/endostatin and inhibit tumor growth in Walker-256 liver cancer[191] (Figure 2).

Combination with chemotherapy

Chemotherapy is not conventionally used in hepatocarcinoma, but chemotherapeutic drugs based TACE is a major treatment for liver cancer. Ban-Zi-Lian (*Sculellaria barbata*) can significantly enhance 5-fluorouracil (5-Fu) to inhibit tumor growth and prolong survival time, improve immune function, and reduce the toxic effects of 5-Fu in the H22 tumor-bearing mice[192]. Ling-Zhi (*Ganoderma lucidum*) is able to inhibit hepatocarcinoma cell proliferation and protect hepatocytes from chemotherapy induced damage[193]. Dong-Chong-Xia-Cao (*Cordyceps sinensis*) may protect H22 hepatocarcinoma bearing mice from chemotherapy induced immunosuppression[194].

Chaiqiyigan granula is potent to enhance inhibitory effects of taxol on hepatocarcinoma growth accompanied by up-regulation of Bax and down-regulation of p53 and VEGF[195]. QHF, an herbal component formula, could reduce cisplatin (DDP)-induced leucopenia, spleen and thymus atrophy, enhance tumor growth inhibition and prolong survival time in H22 bearing mice[196]. Shengmai Injection, a patent herbal drug, is effective to enhance anti-tumor efficacy and reduce toxicity of 5-Fu in H22 hepatocarcinoma[197] (Figure 2).

Reversal of drug resistance

Drug resistance contributes to chemotherapy refractoriness in hepatocarcinoma[198]. To seek effective herbs or herbal components to reverse drug resistance has become one of research focuses in liver cancer study. *Astragalus* polysaccharides have been reported to be potent to enhance anti-tumor effects of adriamycin in H22 hepatocarcinoma by up-regulating IL-1α, IL-2, IL-6, and TNF-α, down-regulating IL-10 and multidrug resistance protein 1 (MDR1)[199]. Astragaloside Ⅱ, another component from Huang-Qi (*Astragalus membranaceus*),

is effective to increase 5-Fu cytotoxicity toward 5-Fu-resistant Bel-7402/Fu cells accompanied by down-regulation of P-gp (P-glycoprotein), phosphorylation of ERK1/2, p38 and JNK[200].

Green tea catechins have been reported to effectively inhibit MDR1 expression, increase intracellular doxorubicin (DOX) accumulation and enhance DOX-induced cell killing activities against BEL-7404/DOX cells[201]. Tetramethylpyrazine, a bioactive constituent isolated from the root of *Ligusticum chuanxiong* Hort, could down-regulate MDR1, multidrug resistance protein 2 (MRP2), MRP3 and MRP5 in adriamycin resistant HepG2 cells[202]. Pseudolaric acid B, polyphyllin D and *Eclipta alba* (Mo-Han-Lian) have been demonstrated to increase drug sensitivity in drug resistant HepG2 hepatoma cells[203-205] (Figure 2).

CONCLUSION

Hepatocarcinoma patients may present Qi-stagnation, damp-heat, blood stasis, Qi-deficiency, Yin-deficiency and other TCM syndromes. Modern treatments such as surgery, TACE and HIFU and other treatments would influence syndrome manifestation in liver cancer patients. Modern technologies have been exploited to elucidate the relation between syndromes and biomedical sciences. Further studies are needed to use those information for herb medication and formulation to improve clinical efficacy of TCM treatment for hepatocarcinoma.

Since TCM pathological factors and syndromes in hepatocarcinoma patients, such as Qi-stagnation, damp-heat, blood stasis, Qi and Yin-deficiency, are also seen in other disease, hepatocarcinoma needs to be recognized and treated as a malignant disease. In addition to syndrome differentiation based treatment, anti-cancer therapy or anti-cancer herb application should be reinforced in the treatment of hepatocarcinoma. Moreover, since most of liver cancer patients receive comprehensive therapy, TCM treatment in those patients should consider the received therapy and accordingly adjust herb medication.

Classic TCM theory and principles have been adopted for hepatocarcinoma prevention study. Chinese herbs with traditional efficacy of tonifying Qi, blood and Yin, soothing liver-Qi stagnation, clearing heat and detoxifying and dissolving stasis, have been demonstrated to be potent to prevent hepatocarcinogenesis. Some classical and modern herbal formulas have been demonstrated to have preventive effects against hepatocarcinogenesis. Further clinical studies are needed to use these achievements to protect high-risk individuals from hepatocarcinogenesis.

Clinical practices have confirmed that TCM is effective to alleviate clinical symptoms, improve QOL and immune function, prevent recurrence and metastasis, delay tumor progression, and prolong survival time in hepatocarcinoma patients. Experimental studies have demonstrated that Chinese herbs and/or herbal formula are potent to induce apoptosis, autophagy, anoikis and cell senescence, arrest cell cycle, regulate immune function, inhibit metastasis and angiogenesis, reverse drug resistance and enhance effects of chemotherapy in hepatocarcinoma.

How to use experimental results to improve clinical efficacy has become an important research subject. For commonly used traditional herbs with anti-cancer effects, the property of Chinese herbs should be firstly considered and medicated by the guidance of TCM principles. For traditionally uncommonly used anti-cancer herbs, such as Mu-Tou-Hui (*Patrinia scabra* Bunge) and She-Mei [*Duchesnea indica* (Andr.) Focke], the property of Chinese herbs and anti-cancer characters of those herbs need to be further studied. In addition, there is a great need to explore the compatibility or combinational application rule of anti-cancer herbs to further improve clinical efficacy of TCM treatment for hepatocarcinoma.

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