

Role of traditional Chinese medicine in the management of patients with hepatocellular carcinoma

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Abstract

Traditional Chinese Medicines (TCMs) have been employed for centuries in the treatment of patients with hepatocellular carcinoma (HCC). Previous reviews of this topic have focused on certain aspects of TCM treatment rather than an overall assessment of their value and mechanisms of action. Both the Chinese and English medical literatures were reviewed to identify where TCM might be of value in the treatment of HCC and the justification for such treatment. TCM treatment corrects the "internal disequilibriums" thought to be responsible for the development, growth, and spread of the tumor. It has also been used to manage symptoms associated with HCC and the adverse effects of chemo- and radiation-therapies. Recent research has documented the precise effects of TCM on tumor biology. There are also increasing efforts to identify which of the many components of TCM herbal remedies are primarily responsible for these beneficial effects. This review outlines the benefits of TCM treatment of HCC and the laboratory data describing their anti-tumor properties.

Key words: Hepatoma; Herbal medicine; Liver disease; Liver; Cancer

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Core tip: Traditional Chinese Medicines (TCMs) are commonly employed by patients with hepatocellular carcinoma (HCC). This review identifies which herbal concoctions are most frequently recommended by TCM authorities. TCMs serve to correct internal imbalances that contribute to HCC. TCMs favorably alter HCC cell biology.

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INTRODUCTION

Traditional Chinese Medicine (TCM) is a comprehensive medical system that utilizes herbal remedies, acupuncture, dietary therapy, exercise, and massage to prevent, treat, and rehabilitate disease states by restoring the internal environments of an individual to a state of equilibrium. It is based on traditional medical theories and the practice experiences of Chinese TCM physicians. The traditional medical theories describe two components of illness: "holism" (the concept of viewing the situation as a whole) and "syndrome differentiation" (the consequences of disrupted holism). Thus, rather than focusing on the tumor *per se*, TCM focuses on correcting the internal disequilibriums responsible for tumor development and progression.

Given the phylogeny of the oncogenic hepatitis B virus (HBV), it can be assumed that hepatocellular carcinoma (HCC) has been prevalent in the Chinese population for centuries^[1]. Hence, Chinese TCM physicians have had extensive experience in identifying, developing, and refining treatments for this potentially lethal tumor. This longstanding experience and commitment to treating HCC is an important feature of TCM. Specifically, unlike "Western Medicine" where effective treatments are identified by the results of prospective, randomized, placebo-controlled trials, in TCM, the value of a particular herbal concoction is gauged by the number of recommendations it has received by TCM authorities over the course of centuries.

MOST COMMONLY EMPLOYED TCMS FOR HCC

TCM physicians have identified various Chinese herbal medicines that represent every category of the Chinese materia medica recognized by the International Organization for Standardization (ISO)^[2]. The majority of these agents are deficiency-supplementing herbs, heat-clearing herbs, and blood-quickening stasis-transforming herbs (Table 1).

The ten most commonly employed individual herbs are provided in Table 2. They are: Poria (Fuling), Rhizoma Atractylodis Macrocephalae (Baizhu), Radix Astragali Mongolici (Huangqi), Herba Hedyotidis (Baihuasheshecao), Radix Glycyrrhizae (Gancao), Radix Bupleuri Chinensis (Chaihu), Radix Codonopsis (Dangshen), Radix Paeoniae Alba (Baishao), Radix Angelicae Sinensis (Danggui) and Carapax Trionycis (Biejia).

Often, combinations of herbs are advocated such

as qi-boosting spleen-supplementing herbs being combined with heat-clearing toxin-resolving herbs, blood-quickening stasis-transforming herbs and/or liver-soothing qi-rectifying herbs (qi is the vital life force that is thought to animate the body internally)^[3]. The ten most commonly advocated combinations of herbs are provided in Table 3.

TCMS FOR THE TREATMENT OF HCC SYMPTOMS

Anorexia, fatigue, weakness, and right upper quadrant discomfort are the most common symptoms of HCC while ascites and jaundice are the most common signs^[4]. TCMS are often used in the treatment of these and the other features listed in Table 4. In a recent cluster analysis performed by Liu *et al*^[4], Endothelium Coreneum Gigeriae Galli (Jineijin) and Fructus Hordei Germinatus (Maiya) were the most commonly-used herbal medicines for treating anorexia; Radix Astragali Mongolici (Huangqi) for fatigue and weakness; Rhizoma Corydalis Yanhusuo (Yanhusuo) and Fructus Toosendan (Chuanlianzi) for right upper quadrant discomfort; Pericarpium Arecae (Dafupi), Polyporus (Zhuling) and Poria (Fuling) for ascites; and Herba Artemisiae Capillaris (Yinchen) for jaundice^[5]. Other herbal medicines used to treat less common symptoms and signs of HCC are also provided in Table 4.

TCM FOR IMPROVED QUALITY OF LIFE AND SURVIVAL IN HCC PATIENTS

The use of TCM to correct disequilibriums in a patient's internal environment has been associated with improved quality of life for HCC patients. For example, the Jianpi Jiedu Decoction has been reported to improve quality of life by attenuating symptoms in 30 patients with advanced HCC^[6]. Similar results have been obtained with other combinations^[7-10].

Other studies have described improved survival. Specifically, compared to untreated controls, treatment with a Ruanganlidan Decoction and Rhizoma Curcumae Longae increased median disease-free survival by approximately 12 mo in 78 HCC patients^[11]. In another study, Qudu Huayu Xiaoji Formula not only improved the quality of life in 77 HCC patients after hepatic arterial chemoembolization, but also prolonged survival by 5-9 mo when compared to 76 patients treated with chemoembolization alone^[12].

TCM AND ADVERSE REACTIONS TO CHEMOTHERAPEUTIC AGENTS

Side effects of chemotherapy are major concerns for cancer patients and often interfere with treatment.

Table 1 Types of herbal medicines and frequency of use in the treatment of patients with hepatocellular carcinoma

Category	Relative frequency	Category	Relative frequency
Herbs that supplement deficiency: Baizhu, Huangqi, Dangshen, Danggui, Shanyao, Gancao, Baishao, Biejia	27.70%	Herbs that drain downwards: Dahuang, Yuanhua	1.37%
Herbs that clear the heat: Baihuasheshecao, Banzhilian, Shengdihuang, Zhizi, Huangqin, Qinghao	19.26%	Herbs that astringe: Wuweizi, Shanzhuyu	1.01%
Herbs that invigorate blood and dissolve stasis: Ezhu, Danshen, Yujin, Tubiechong	13.67%	Herbs that counteract toxins, kill parasites and relieve itching: Fengfang	0.68%
Herbs that promote urination and percolate dampness: Fuling, Yiyiren, Yinchén, Cheqianzi, Yumixu	12.04%	Herbs that warm the interior: Wuyao	0.54%
Herbs that rectify qi: Zhiqiao, Chenpi	8.39%	Herbs that expel wind and damp: Sangjisheng, Qinjiao	0.46%
Herbs that release the exterior: Chaihu, Guizhi	4.14%	Herbs that calm the mind: Suanzaoren, Longgu	0.42%
Herbs that promote digestion: Jineijin	3.18%	Herbs that calm the liver and extinguish wind: Muli, Wugong	0.25%
Herbs that relieve cough, dissolve phlegm and calm panting: Banxia, Tinglizi, Walengzi	2.94%	Herbs that open the orifices: Shexiang	0.11%
Herbs that stanch bleeding: Sanqi, Xianhecao, Baimaogen	1.91%	Herbs that expel parasites: Binglang	0.08%
Herbs that transform dampness: Houpo	1.86%	Herbs that induce vomit: Changshan	0.02%

Table 2 The most frequently prescribed herbal medicines used in the treatment of patients with hepatocellular carcinoma

Herb name	Relative frequency	Herb name	Relative frequency
Poria (Fuling)	5.20%	Radix Angelicae Sinensis (Danggui)	2.35%
Rhizoma Atractylodis Macrocephalae (Baizhu)	5.20%	Carapax Trionycis (Biejia)	2.22%
Radix Astragali Mongolici (Huangqi)	4.07%	Radix Bupleuri Chinensis (Chaihu)	3.66%
Herba Hedyotidis (Baihuasheshecao)	3.75%	Radix Codonopsis (Dangshen)	3.26%
Radix Glycyrrhizae (Gancao)	3.71%	Radix Paeoniae Alba (Baishao)	3.03%

Numerous TCM herbs have been identified that reduce the side effects and non-tumor toxicity of chemotherapeutics. For example, Ciji Hua'ai Baosheng Granule Formula (CHBGF) attenuates the decreases in white blood cell and platelet counts of H₂₂ hepatoma transplanted tumor caused by chemotherapy^[13]. Combining Rhizoma Zingiberis Recens (Shengjiang) and Rhizoma Phragmitis (Lugen) reduces the vomiting caused by chemotherapy in H₂₂ hepatoma carcinoma-bearing mice^[14], and Danggui Beimu Kushen attenuates cisplatin toxicity (in the same animal model). Other TCMs such as Panaxan, Fufang Ejiao Jiang, Lianqi Capsule, and the aqueous extract of Fructus Akebiae (Bayueza) have also been reported to reduce side effects and improve the efficacy of chemotherapy for HCC in H₂₂ hepatoma bearing mice^[15-18]. Compared to chemotherapy alone, Tremella Polysaccharide, extracted from Polyporus (Zhuling), improved quality of life and physical activity and attenuated fatigue, nausea, vomiting, constipation, diarrhea, and white blood cell counts during chemotherapy in 50 patients^[19]. Jianpi Jiedu Formula minimized hepatic dysfunction following transarterial chemoembolization (TACE) treatment in 16 patients^[20]. Similarly, the Zipi Decoction was associated with improved hepatic function following TACE when compared to TACE alone^[21]. Jian Pi Li Qi Decoction in 52 patients and Jiedu Granules combined with Cinobufacini in 60 patients alleviated signs and symptoms of the

postembolization syndrome following TACE^[22]. Finally, it should be noted that on occasion, TCM can adversely affect patient outcomes when TCM and chemotherapy drugs interact^[23].

TCM AND HCC TUMOR BIOLOGY

Recent developments in molecular and cell biology have provided important insights into the pathogenesis and course of HCC. They have also provided investigators with an opportunity to identify the mechanisms whereby TCM impacts HCC. To date, such research has focused on HCC proliferative activity, apoptosis, metastasis, angiogenesis, immune reactivity, and multidrug resistance.

The effects of TCM on the proliferative activity and growth of malignant hepatocytes and tumors

A large number of herbs have been reported to inhibit malignant hepatocyte proliferation and tumor growth. In many instances, the precise mechanisms and signaling pathways have also been identified. For example, Akebia trifoliata (Thunb.) and Koidz (Sanyemutong) seed extract inhibited the proliferation of various human HCC cell lines *via* induction of endoplasmic reticulum stress *in vitro*^[24] whereas the ethyl acetate extraction from a Chinese herbal formula, Jiedu Xiaozheng Yin inhibited proliferative activity by suppression of the

Table 3 Descending frequency of herbal medicine combinations used in the treatment of patients with hepatocellular carcinoma

Precedence	Herbal medicine combinations
1	Rhizoma Atractylodis Macrocephalae (Baizhu) and Poria (Fuling)
2	Radix Astragali Mongolici (Huangqi) and Rhizoma Atractylodis Macrocephalae Baizhu)
3	Radix Astragali Mongolici (Huangqi) and Radix Codonopsis (Dangshen)
4	Radix Astragali Mongolici (Huangqi) and Radix Angelicae Sinensis (Danggui)
5	Radix Astragali Mongolici (Huangqi) and Poria (Fuling)
6	Rhizoma Atractylodis Macrocephalae (Baizhu) and Radix Curcumae Wenyujin (Yujin)
7	Rhizoma Atractylodis Macrocephalae (Baizhu) and Radix Bupleuri Chinensis (Chaihu)
8	Rhizoma Atractylodis Macrocephalae (Baizhu) and Radix Glycyrrhizae (Gancao)
9	Rhizoma Atractylodis Macrocephalae (Baizhu) and Pericarpium Citri Reticulatae (Chenpi)
10	Rhizoma Atractylodis Macrocephalae (Baizhu) and Radix Codonopsis (Dangshen)

Table 4 Herbal medicines and the frequency of their use in treating symptoms and signs associated with hepatocellular carcinoma

Symptoms and signs	Herb and frequency of use (n)
Anorexia	Endothelium Coreneum Gigeriae Galli (Jineijin) (18), Fructus Hordei Germinatus (Maiya) (12), Fructus Amomi (Sharen) (9), stir-baking Fructus Hordei Germinatus et Massa Fermentata Medicinalis (Jiaosanxian) (7), Fructus Setariae Germinatus (Guya) (6), Massa Medicata Fermentata (Shenqu) (5) and Fructus Crataegi Pinnatifidae (Shanzha) (5)
Fatigue	Radix Astragali Mongolici (Huangqi) (23) and Radix Codonopsis (Dangshen) (14)
Discomfort	Rhizoma Corydalis Yanhusuo (Yanhusuo) (15), Fructus Toosendan (Chuanlianzi) (13), Radix Curcumae Wenyujin (Yujin) (10), Olibanum (Ruxiang) (9), Myrrha (Moyao) (7), Fructus Citri Sarcodactylis (Foshou) (7), Radix Aucklandiae (Muxiang) (5) and Rhizoma Cyperi (Xiangfu) (5)
Ascites	Pericarpium Arecae (Dafupi) (30), Polyporus (Zhuling) (22), Poria (Fuling) (18), Rhizoma Alismatis (Zexie) (13), Semen Plantaginis (Cheqianzi) (8) and Cortex Magnoliae Officinalis (Houpo) (5)
Jaundice	Herba Artemisiae Capillaris (Yinchen) (37), Rhizoma Polygoni Cuspidati (Huzhang) (13), Radix et Rhizoma Rhei Palmati (Dahuang) (11), Herba Hyperici Japonici (Tianjihuang) (8), Fructus Gradeniae (Zhizi) (8), Herba Lysimachiae (Jinqiancao) (7), Radix Paeoniae Rubra (Chishao) (6) and Radix Scutellariae Baicalensis (Huangqin) (6)
Abdominal distention	Fructus Aurantii Submaturus (Zhiqiao) (11), Cortex Magnoliae Officinalis (Houpo) (8), Semen Raphani Sativi (Laifuzi) (7), Pericarpium Citri Reticulatae Viride (Qingpi) (6), Radix Aucklandiae (Muxiang) (6), Fructus Amomi (Sharen) (5) and Fructus Aurantii Immaturus (Zhishi) (5)
Nausea and vomiting	Caulis Bambusae in Taeniam (Zhuru) (27), Rhizoma Pinelliae (Banxia) (19), Flos Inulae (Xuanfuhua) (17), Fructus Amomi (Sharen) (10), Ochra Haematitum (Daizheshi) (7) and Pericarpium Citri Reticulatae (Jupi) (6)
Fever	Gypsum Fibrosum (Shigao) (9), Cortex Moutan Radicis (Mudanpi) (8), Radix Bupleuri Chinensis (Chaihu) (8), Herba Artemisiae Annuae (Qinghao) (6), Rhizoma Anemarrhenae (Zhimu) (6) and Fructus Gradeniae (Zhizi) (6)
Diarrhea	Poria (Fuling) (7), Rhizoma Alismatis (Zexie) (7), Semen Euryales (Qianshi) (6) and Fructus Schisandrae Chinensis (Wuweizi) (5)
Constipation	Radix et Rhizoma Rhei Palmati (Dahuang) (12), Fructus et Semen Trichosanthis Kirilowii (Gualou) (6), Semen Pruni Japonicae (Yuliren) (5) and Fructus Cannabis (Huomaren) (5)

polycomb gene product Bmi1 and Wnt/ β -catenin signaling and inducing G0/G1 phase arrest *in vitro* and *in vivo*^[25,26]. Coptischinensis (Huanglian) restrained HepG2 cell proliferation through activation of the the NAG-1 gene enzyme *in vitro*^[27].

Other TCM herbs have been reported to inhibit malignant hepatocyte proliferative activity and tumor growth through mechanisms that have yet to be identified. Of these, Bufalin, a component of Venenum Bufonis (Chansu), inhibited both proliferation and invasion of HCC cells *in vitro*^[28], and Chaiqiyan granula enhanced Taxol-induced growth inhibition of HCC xenografts in nude mice^[29]. Other herbal medicine extracts that have been reported to possess tumor growth inhibiting properties *via* yet to be defined mechanisms include Jianpi Huayu Formula, which inhibited BEL7402 cell proliferation *in vitro*^[30], Compound Recipe Kushen SMMC, which inhibited 7721 cell proliferation *in vitro*^[31], and Fuzheng

Yiliu Granule, which inhibited PLC tumor growth in H₂₂ hepatoma-bearing ICR mice and the HepG2 cell line^[32].

The effects of TCM on apoptosis and autophagy of malignant hepatocytes

Dysregulation of apoptosis and autophagy are important components of tumor development, often resulting from activation of oncogenes and/or mutations in tumor suppressor genes. Thus, much effort has been expended on identifying TCM herbs that induce malignant hepatocyte apoptosis. Kangai Fuzheng Prescription was found to promote apoptosis and inhibit the growth of human hepatoma SMMZ-7721 cells by downregulating p53 gene expression *in vitro*^[33]. TCM matrine, a component of Radix Sophorae Flavescentis (Kushen), induced apoptosis and cell arrest by altering Bcl-2, Bax, and miR122a expression in human HepG2 cells and murine HCC cells^[34,35]. Quercetin, an extract

from multiple herbal medicines, promoted apoptosis in the same HepG2 cells by increasing the transcription of the apoptosis-related *fas* gene^[36]. *Ligustrum lucidum* Aitfruit (Nüzhenzi) extract could induce apoptosis and cell senescence through upregulation of p21 in human HCC cell lines^[37]. Finally, modified Yi Guan Jian, a Chinese herbal formula, induced apoptosis in Bel-7402 cells^[38] and *Rhizoma Panacis Majoria* (Zhuzishen) in H22 hepatoma cells^[39].

In addition to inducing apoptosis, Baicalein, from *Radix Scutellariae Baicalensis* (Huangqin), enhanced autophagy *via* increasing endoplasmic reticulum stress in HCC cells^[40]. Similarly, Arenobufagin (Chansu), a natural bufadienolide from toad venom, induced apoptosis and autophagy in human HCC cells but through inhibition of the PI3K/Akt/mTOR pathway in human HCC cells^[41].

The effects of TCM on malignant hepatocyte metastases

Controlling HCC metastases is an important strategy for preventing tumor recurrence. Various TCM herbs have been reported to possess this property. Specifically, Sini-San inhibited HBx-induced migration and invasiveness of HCC cells by inhibiting multiple signal transduction pathways including ERK/phosphatidylinositol 3-kinase/Akt upstream of NF- κ B and AP-1 in human HCC cells^[42] while Biejiajian Pill suppressed the invasiveness of HepG2 cells by inhibiting the Wnt/ β -catenin pathway in HCC cells^[43]. Jinlong Capsule decreased the adhesive ability of highly metastatic MHCC97H cells *in vitro* and thereby significantly inhibited their movement and invasion^[44].

In animal studies, Ginsenoside Rg3 from Ginseng (Renshen) inhibited the growth and metastasis of the highly metastatic human LCI-D20 cells in nude mice. This effect was ascribed to regulating the expression of nm23 and CD44 proteins^[45]. By inhibiting SMMC-7721 cell invasion, *Radix Salviae Miltiorrhizae* (Danshen) decreased intrahepatic and distant metastasis of these cells in nude mice^[46]. Another TCM that inhibits malignant hepatocyte metastases is Berberine, which inhibited the growth and development of spontaneously developed lung metastases in an orthotopic model of HCC (MHCC-97L) in mice by suppressing Id-1 expression^[47].

The effects of TCM on HCC angiogenesis

HCC survival, growth, and metastases are dependent on new blood vessel growth or angiogenesis (Figure 1). TCM herbs that inhibit HCC angiogenesis include the alkaloids of *Rubus alceifolius* Poir (Cuyexuangouzi) and *Livistonachinensis* seeds (Pukuizi), which interfere with Notch signaling in a mouse model of HCC^[48,49]. Resveratrol [typically extracted from *Rhizoma Polygoni Cuspidati* (Huzhang) or *Fructus Mori* (Sangshen)] decreases microvessel density of transplanted hepatic tumors in nude mice and inhibits tumor growth^[50]. By significantly reducing vascular endothelial growth factor

expression, *Celastrus orbiculatus* Thunb (Nansheteng) inhibited Hep-G2 induced tumor growth in orthotopic nude mice^[51]. Finally, Qinggan Huayu Formula has been reported to inhibit tumor development and growth by reducing vascular endothelial growth factor and transforming growth factor- β 1 protein expression and neovascularization in HCC rats^[52].

The effects of TCM on the immunologic response to HCC

In the absence or setting of a suboptimal immune response, tumor cell growth, metastasis, and rates of recurrence are enhanced. Thus, the status of natural killer cells, T lymphocyte subpopulations such as CD3⁺, CD4⁺ and CD8⁺, and pro- as well as anti-inflammatory cytokines are important, and the ability of TCM to enhance the immune response to HCC would be of therapeutic value. *Ganoderma lucidum* polysaccharides (GLPS) is an extract from *Ganoderma lucidum* (Lingzhi) that significantly increases the ratio of T effector to regulatory T cells and suppresses tumor growth in HCC-bearing mice^[53]. Moreover, GLPS eliminates regulatory T cells suppression of T effector proliferation resulting in increased pro-inflammatory IL-2 secretion. GLPS has also been reported to inhibit T cell Notch1 and FoxP3 expression by increasing miR-125b expression in hepatoma-bearing mice^[53]. Another TCM with immunomodulant properties is *Radix Astragali Mongolici* (Huangqi), a polysaccharide, which inhibits the growth of mouse HCC HepA by promoting pro-inflammatory TNF- α and IFN- γ production^[54]. Combining Jiedu Xiaozheng Yin and Fuzheng Yiliu Formula improved the immune function of mice with H22 HCC by increasing CD3⁺ and CD3⁺/CD4⁺^[55]. Shaoyao Ruangan Recipe, Biejiajian Pill, Ginsenoside Rg3, *Fructus Lycii* (Gouqizi) polysaccharide, and *Fructus Schisandrae Chinensis* (Wuweizi) polysaccharides are other herbal medications that have been reported to inhibit HCC by enhancing the host's immune responsiveness in HCC-bearing mice^[56-60].

The effects of TCM on the multidrug resistance of malignant hepatocytes

Increased expression of multidrug resistance (MDR) protein activity, the family of transporters responsible for exporting xenobiotics from within cells, is considered the principal explanation for the failure of chemotherapy in HCC treatment. Many TCM herbs have been reported to reverse MDR expression and/or activity. For example, Tetramethylpyrazine, a bioactive constituent isolated from the root of *Ligusticum chuanxiong* Hort (Chuanxiong) downregulated P-gp, MRP2, MRP3, and MRP5 expression in HCC BEL-7402/ADM cells^[61]. Bufalin, extracted from *Venenum Bufonis* (Chansu) and *Hedyotis diffusa* (Baihuasheshicao) injection, achieved the same effect in BEL-7402/5-FU cells^[62-63], and *Hirudo* (Shuizhi) extract, Qizhu Decoction, *Shehuang Xiaoliu*

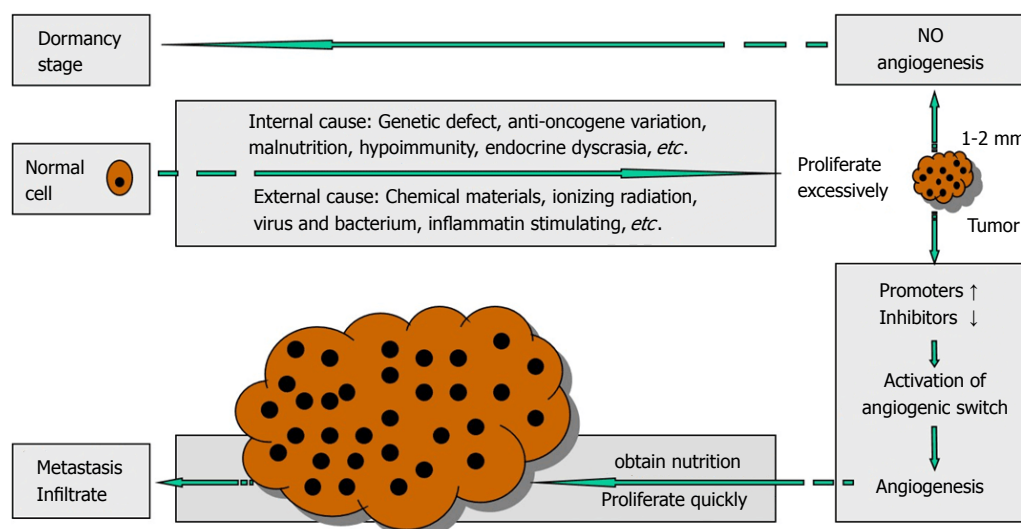


Figure 1 Solid tumor's occurrence and angiogenesis.

Decoction, Jianpi Huayu Formula and Quercetin all reversed MDR activity in HCC tissues^[64-68].

CONCLUSION

Although much progress has been made in our utilization and understanding of TCMs for the treatment of HCC, additional experimentation and research is still required. Clearly, no single herbal medicine, active component, or compound recipe has been identified to be curative. Moreover, the mechanism(s) involved in achieving the benefits described are multiple and complex. Nonetheless, empiric and experimental data suggest that TCM is effective in limiting symptoms, reducing treatment associated side effects, inhibiting tumor growth, and altering key intracellular signaling pathways. While a combination of TCM and Western medicine may evolve as the optimal approach to treating HCC, certain challenges remain. Principal amongst these is the need for Western Medicine physicians to consider and where appropriate accept the concept of "holism" for cancer treatment. These physicians must also be willing to consider empiric findings, albeit of century's duration, as an additional measure of efficacy, particularly for compounds such as TCM herbs that due to their unique fragrance, do not always lend themselves to testing in placebo-controlled clinical trials.

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REFERENCES

1 Wallace MC, Preen D, Jeffrey GP, Adams LA. The evolving epi-

demology of hepatocellular carcinoma: a global perspective. *Expert Rev Gastroenterol Hepatol* 2015; **9**: 765-779 [PMID: 25827821 DOI: 10.1586/17474124.2015.1028363]

2 Liao LP, Xu MQ, Wu PK, Zeng QM, Yi BX, Xu GL. A study on classification of Chinese medicine by ISO and GB coding technology and the rules. *World Chin Med* 2015; **10**: 772-775 [DOI: 10.3969/j.issn.1673-7202.2015.05.035]

3 Yang JM, Han LT, Ren JG, Li JM, Li HH. Literature analysis of traditional Chinese medicine commonly used for treatment of liver cancer. *World Chin Med* 2013; **8**: 1150-1151

4 Liu X, Li N. [Regularity analysis on clinical treatment in primary liver cancer by traditional Chinese medicine]. *Zhongguo Zhongyao Zazhi* 2012; **37**: 1327-1331 [PMID: 22803386 DOI: 10.4268/cjcm20120933]

5 Sun M, Chen Q. Investigate the relations between the TCM patterns of primary hepatic cancer and ultrasonography results. *Hubei J Tradit Chin Med* 2011; **33**: 20-21

6 Lao GQ, Chen F, Shi ZY, He XH, Luo JH, Huang RH, Liang DR, Chen JJ. Effect on life quality by Jianpi Jiedu Decoction in the treatment of advanced stage of hepatocellular carcinoma. *Chin J Chin Med* 2012; **27**: 1083-1084 [DOI: 10.16368/j.issn.1674-8999.2012.09.006]

7 Li XL, Lan MY, Wu LJT, Zhao XQ, Kan JG. Clinical therapeutic effect observation of Compound Recipe Kushen Injection treating the middle or advanced liver cancer patients. *J Chifeng Univ (Nat Sci Edition)* 2014; **30**: 135-136 [DOI: 10.13398/j.cnki.issn1673-260x.2014.22.057]

8 Huang JD, Wei AX. Impact of Jianpi Tiaogan Tang on life quality of patients with terminal primary liver cancer. *World Chin Med* 2014; **9**: 1319-1321 [DOI: 10.3969/j.issn.1673-7202.2014.10.019]

9 Chen QS, Chen Y, Pei RQ, Huang WZ, Li CY, Zhou B, Chen YY. Clinical observation of 30 cases of late-stage primary hepatic cancer treated with Jianpi Yiliu Decoction. *World J Integr Tradit West Med* 2013; **8**: 368-370 [DOI: 10.13935/j.cnki.sjzx.2013.04.012]

10 Feng GF, Chen R, Chen WZ. Observation on treating ascites in primary liver carcinoma by Ascending Lucidity-Descending Turbidity Decoction. *Liaoning J Tradit Chin Med* 2015; **42**: 1285-1286 [DOI: 10.13192/j.issn.1000-1719.2015.07.054]

11 Si T, Ning XJ, Yang JQ, Feng XB, Shi Y, Li R. Ruanganlidan decoction on disease-free survival after a radical liver resection. *J Changchun Univ Chin Med* 2015; **31**: 145-148 [DOI: 10.13463/j.cnki.cczyy.2015.01.050]

12 Lu YX, Lu XQ, Wu FS, Tan ZW, Mo YJ, Lai L. Effect of Qudu

- Huayu Xiaoji formula on life span and life quality of patients with primary hepatocellular carcinoma in middle/advanced stage after interventional therapy. *J New Chin Med* 2016; **48**: 153-155 [DOI: 10.13457/j.cnki.jncm.2016.09.069]
- 13 **Xi S**, Hong R, Huang J, Lu D, Qian L, Li P, Wen L, Wang Y. Effects of Ciji Hua'ai Baosheng granule formula (CHBGF) on life time, pathology, peripheral blood cells of tumor chemotherapy model mouse with H22 hepatoma carcinoma cells. *Afr J Tradit Complement Altern Med* 2014; **11**: 94-100 [PMID: 25392588 DOI: 10.4314/ajtcam.v11i4.16]
 - 14 **Hu J**, Wang HL, Zhang H, Li ZZ, Yue W, Zhang JG. The detoxification and synergistic effect of zingiber and rhizoma composite on radiotherapy and chemotherapy. *J Taishan Med College* 2014; **35**: 848-850 [DOI: 10.3969/j.issn.1004-7115.2014.09.003]
 - 15 **Jia YP**, Zhou DS, Sun C, Qu BE. Efficiency-enhancing and toxicity-reducing effects of ginseng polysaccharide on cyclophosphamide treatment of mouse hepatoma. *Acta Lab Anim Sci Sin* 2013; **21**: 61-64
 - 16 **Li M**, Ma HY, Shen JD, Li YC. Effects of Fufang Ejiao Jiang enhances efficacy and reduces toxicity of 5-Fu in hepatoma H22-bearing mice. *Chin J Exp Tradit Med Form* 2012; **18**: 216-219 [DOI: 10.13422/j.cnki.syfjx.2012.20.065]
 - 17 **Wang HZ**, Mao HL. Lian Qi Capsules enhances efficacy and reduces toxicity of chemotherapy in hepatoma H22-bearing mice. *Chin J Med Guide* 2013; **15**: 1033-1034, 1037
 - 18 **Bai X**, Guan BS, Sun YN, Zhang LY, Ji HT, Zhang T. Effect of aqueous extract of Fructus Akebiae (Bayuezhua) on immune function of hepatoma H22-bearing mice. *Chin J Geront* 2015; **35**: 1946-1948 [DOI: 10.3969/j.issn.1005-9202.2015.07.096]
 - 19 **Pang LF**. Clinical study about parenteral solution of Tremella Polysaccharide improving quality of life of patients with liver cancer during chemotherapy. *J Hubei Univ Chin Med* 2014; **16**: 85-86 [DOI: 10.3969/j.issn.1008-987x.2014.04.31]
 - 20 **Xue WW**, Zhu CL. Clinical research of JianpiJiedu Formula preventing and treating hepatic functional lesion after chemoembolization for patients with primary hepatic carcinoma. *J Shandong Univ TCM* 2013; **37**: 392-394 [DOI: 10.16294/j.cnki.1007-659x.2013.05.011]
 - 21 **Ding JP**. The retrospective study of advanced hepatocellular carcinoma by treated with Zipi decoction combined with TACE. *J Pract Tradit Chin Inter Med* 2015; **29**: 9-11 [DOI: 10.13729/j.issn.1671-7813.2015.02.04]
 - 22 **Xu L**, Wang S, Zhuang L, Lin J, Chen H, Zhu X, Bei W, Zhao Q, Wu H, Meng Z. Jian Pi Li Qi Decoction Alleviated Postembolization Syndrome Following Transcatheter Arterial Chemoembolization for Hepatocellular Carcinoma: A Randomized, Double-Blind, Placebo-Controlled Trial. *Integr Cancer Ther* 2016; **15**: 349-357 [PMID: 26590124 DOI: 10.1177/1534735415617020]
 - 23 **Yap KY**, See CS, Chan A. Clinically-relevant chemotherapy interactions with complementary and alternative medicines in patients with cancer. *Recent Pat Food Nutr Agric* 2010; **2**: 12-55 [PMID: 20653549 DOI: 10.2174/2212798411002010012]
 - 24 **Lu WL**, Ren HY, Liang C, Zhang YY, Xu J, Pan ZQ, Liu XM, Wu ZH, Fang ZQ. Akebia trifoliata (Thunb.) Koidz Seed Extract Inhibits the Proliferation of Human Hepatocellular Carcinoma Cell Lines via Inducing Endoplasmic Reticulum Stress. *Evid Based Complement Alternat Med* 2014; **2014**: 192749 [PMID: 25389441 DOI: 10.1155/2014/192749]
 - 25 **Chen XZ**, Cao ZY, Li JN, Hu HX, Zhang YQ, Huang YM, Liu ZZ, Hu D, Liao LM, Du J. Ethyl acetate extract from Jiedu Xiaozheng Yin inhibits the proliferation of human hepatocellular carcinoma cells by suppressing polycomb gene product Bmi1 and Wnt/ β -catenin signaling. *Oncol Rep* 2014; **32**: 2710-2718 [PMID: 25333742 DOI: 10.3892/or.2014.3541]
 - 26 **Cao Z**, Lin W, Huang Z, Chen X, Zhao J, Zheng L, Ye H, Liu Z, Liao L, Du J. Ethyl acetate extraction from a Chinese herbal formula, Jiedu Xiaozheng Yin, inhibits the proliferation of hepatocellular carcinoma cells via induction of G0/G1 phase arrest in vivo and in vitro. *Int J Oncol* 2013; **42**: 202-210 [PMID: 23165653 DOI: 10.3892/ijo.2012.1703]
 - 27 **Auyeung KK**, Ko JK. Coptis chinensis inhibits hepatocellular carcinoma cell growth through nonsteroidal anti-inflammatory drug-activated gene activation. *Int J Mol Med* 2009; **24**: 571-577 [PMID: 19724899]
 - 28 **Qiu DZ**, Zhang ZJ, Wu WZ, Yang YK. Bufalin, a component in Chansu, inhibits proliferation and invasion of hepatocellular carcinoma cells. *BMC Complement Altern Med* 2013; **13**: 185 [PMID: 23870199 DOI: 10.1186/1472-6882-13-185]
 - 29 **You M**, Luo M, Liao W, Hu S, Xu W, Jing L. [Chaiqiyan granule enhances Taxol-induced growth inhibition of hepatocellular carcinoma xenografts in nude mice: an in vivo fluorescence imaging study]. *Nanfang Yike Daxue Xuebao* 2012; **32**: 1042-1045 [PMID: 22820595]
 - 30 **Wang CJ**, Liu YZ, Xu XM. Influence of JianpiHuayu Recipe serum on cell proliferation of human hepatocellular carcinoma Bel-7402. *China Clin Rehabil* 2006; **10**: 82-84
 - 31 **Jiang ZY**, Hua HQ, Qin SK, Yang AZ. Effect of Compound Recipe Kushen Injection on cell proliferation and cycle of human hepatocellular carcinoma SMMC-7721. *Jilin J Tradit Chin Med* 2011; **31**: 690-692 [DOI: 10.13463/j.cnki.jlzyy.2011.07.049]
 - 32 **Cao ZY**, Chen XZ, Liao LM, Peng J, Hu HX, Liu ZZ, Du J. Fuzheng Yiliu Granule inhibits the growth of hepatocellular cancer by regulating immune function and inducing apoptosis in vivo and in vitro. *Chin J Integr Med* 2011; **17**: 691-697 [PMID: 21910071 DOI: 10.1007/s11655-011-0847-3]
 - 33 **Li LH**, Pi WX, Cheng HB, Yu JH, Zhang X, Zhang YH. Inhibiting effect and mechanism of Kangai Fuzheng Prescription (ALC) for human hepatoma SMMC-7721 cell and expression of P53. *Niaoning J Tradit Chin Med* 2010; **37**: 2215-2217 [DOI: 10.13192/j.ljtc.2010.11.140.yelh.064]
 - 34 **Zhou W**, Xu X, Gao J, Sun P, Li L, Shi X, Li J. TCM matrine induces cell arrest and apoptosis with recovery expression of the hepatocellular carcinoma-specific miR122a in human hepatocellular carcinoma Hep G2 cell line. *Int J Clin Exp Med* 2015; **8**: 9004-9012 [PMID: 26309553]
 - 35 **Ma L**, Wen S, Zhan Y, He Y, Liu X, Jiang J. Anticancer effects of the Chinese medicine matrine on murine hepatocellular carcinoma cells. *Planta Med* 2008; **74**: 245-251 [PMID: 18283616 DOI: 10.1055/s-2008-1034304]
 - 36 **Zhao XL**, Xu GC, He LM, Ma L. Apoptosis of human HepG2 cells induced by Guercetin. *Pract J Cardiac Cereb Pneum Vasc Dis* 2010; **18**: 310-311
 - 37 **Hu B**, Du Q, Deng S, An HM, Pan CF, Shen KP, Xu L, Wei MM, Wang SS. Ligustrum lucidum Ait. fruit extract induces apoptosis and cell senescence in human hepatocellular carcinoma cells through upregulation of p21. *Oncol Rep* 2014; **32**: 1037-1042 [PMID: 25017491 DOI: 10.3892/or.2014.3312]
 - 38 **Hu B**, An HM, Shen KP, Xu L, Du Q, Deng S, Wu Y. Modified Yi Guan Jian, a Chinese herbal formula, induces anoikis in Bel-7402 human hepatocarcinoma cells in vitro. *Oncol Rep* 2011; **26**: 1465-1470 [PMID: 21822542 DOI: 10.3892/or.2011.1414]
 - 39 **Chen T**, Hu W, Cui BP, Li JH. Panaxjapclusvar inhibition of proliferation of H22 cells in mice and its mechanism of action. *World Chin J Digest* 2007; **15**: 2597-2601
 - 40 **Wang Z**, Jiang C, Chen W, Zhang G, Luo D, Cao Y, Wu J, Ding Y, Liu B. Baicalein induces apoptosis and autophagy via endoplasmic reticulum stress in hepatocellular carcinoma cells. *Biomed Res Int* 2014; **2014**: 732516 [PMID: 24995326 DOI: 10.1155/2014/732516]
 - 41 **Zhang DM**, Liu JS, Deng LJ, Chen MF, Yiu A, Cao HH, Tian HY, Fung KP, Kurihara H, Pan JX, Ye WC. Arenobufagin, a natural bufadienolide from toad venom, induces apoptosis and autophagy in human hepatocellular carcinoma cells through inhibition of PI3K/Akt/mTOR pathway. *Carcinogenesis* 2013; **34**: 1331-1342 [PMID: 23393227 DOI: 10.1093/carcin/bgt060]
 - 42 **Lin HJ**, Kao ST, Siao YM, Yeh CC. The Chinese medicine Sini-San inhibits HBx-induced migration and invasiveness of human hepatocellular carcinoma cells. *BMC Complement Altern Med* 2015;

- 15: 348 [PMID: 26446078 DOI: 10.1186/s12906-015-0870-6]
- 43 **Wen B**, Sun H, He S, Cheng Y, Jia W, Fan E, Pang J. [Effects of Biejiajian Pills on Wnt signal pathway signal molecules β -catenin/TCF4 complex activities and downstream proteins cyclin D1 and MMP-2 in hepatocellular carcinoma cells]. *Nan Fang Yi Ke Da Xue Xue Bao* 2014; **34**: 1758-1762 [PMID: 25537897]
- 44 **Li LX**, Ye SL, Wang YH, Li JS, Sun RX, Xue Q, Chen J, Gao DM, Zhao Y. Inhibiting effect of Jinlong Capsule on high-metastatic human hepatocellular carcinoma cell lines. *Chin Hepatol* 2011; **16**: 240-241 [DOI: 10.14000/j.cnki.issn.1008-1704.2011.03.001]
- 45 **Hua HQ**, Shen XK, Qin SK, Chen HY. Anti-metastatic and anti-invasive ability of ginsenoside Rg3 on homotopic transplantation nude mouse model of human hepatocellular carcinoma cells. *Chin Clin Oncol* 2007; **12**: 897-901
- 46 **Sun J**, Zhou X, Liu Y. [Study on preventive and therapeutic effect of radix salviae miltiorrhizae on recurrence and metastasis of liver cancer]. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 1999; **19**: 292-295 [PMID: 11783245]
- 47 **Tsang CM**, Cheung KC, Cheung YC, Man K, Lui VW, Tsao SW, Feng Y. Berberine suppresses Id-1 expression and inhibits the growth and development of lung metastases in hepatocellular carcinoma. *Biochim Biophys Acta* 2015; **1852**: 541-551 [PMID: 25496992 DOI: 10.1016/j.bbdis.2014.12.004]
- 48 **Zhao J**, Lin W, Cao Z, Zhuang Q, Zheng L, Peng J, Hong Z. Total alkaloids of *Rubus alceifolius* Poir inhibit tumor angiogenesis through suppression of the Notch signaling pathway in a mouse model of hepatocellular carcinoma. *Mol Med Rep* 2015; **11**: 357-361 [PMID: 25333354 DOI: 10.3892/mmr.2014.2702]
- 49 **Lin W**, Zhao J, Cao Z, Zhuang Q, Zheng L, Zeng J, Hong Z, Peng J. *Livistona chinensis* seeds inhibit hepatocellular carcinoma angiogenesis in vivo via suppression of the Notch pathway. *Oncol Rep* 2014; **31**: 1723-1728 [PMID: 24573440 DOI: 10.3892/or.2014.3051]
- 50 **Sun ZJ**, Yu HB, Zhang Y, Liu XG, Du LX. The effects of Resveratrol on growth and angiogenesis of HepG2 tumor model in vivo. *Shaanxi Med J* 2010; **39**: 279-281
- 51 **Wang M**, Zhang X, Xiong X, Yang Z, Sun Y, Yang Z, Hoffman RM, Liu Y. Efficacy of the Chinese traditional medicinal herb *Celastrus orbiculatus* Thunb on human hepatocellular carcinoma in an orthotopic fluorescent nude mouse model. *Anticancer Res* 2012; **32**: 1213-1220 [PMID: 22493351]
- 52 **Yin F**, Yao SK, Wu XM, Gao HS. Effect of Qinggan Huayu Decoction (QHD) on angiogenesis of hepatocellular carcinoma in rats. *Pharmacol Clin Chin Mater Medica* 2005; **21**: 29-32 [DOI: 10.13412/j.cnki.zyyl.2005.01.014]
- 53 **Li A**, Shuai X, Jia Z, Li H, Liang X, Su D, Guo W. Ganoderma lucidum polysaccharide extract inhibits hepatocellular carcinoma growth by downregulating regulatory T cells accumulation and function by inducing microRNA-125b. *J Transl Med* 2015; **13**: 100 [PMID: 25889022 DOI: 10.1186/s12967-015-0465-5]
- 54 **Xu DJ**, Chen MZ. Antitumor activity of APS and its mechanism of action. *Chin Hosp Pharm J* 2005; **25**: 923-925
- 55 **Chen XZ**, Cao ZY, Yang JL, Du J. Effects of Chinese medicine compound recipe on apoptosis and immune function of subcutaneous transplanted tumor with H22hepatic carcinoma. *Fujian J Tradit Chin Med* 2009; **40**: 52-54 [DOI: 10.13260/j.cnki.jfjt-cm.009689]
- 56 **Sun Y**, Zhang AQ, Gao FY. Immune effect of Shaoyao Ruangan Recipe on hepatocarcinoma in tumor-bearing H22 mice and its effect on VEGF and PCNA expression. *J Emerg Tradit Chin Med* 2015; **24**: 590-592 [DOI: 10.3969/j.issn.1004-745X.2015.04.008]
- 57 **Luo QD**, Wang YH, Zhao HY, Wang B, Du FX, Deng FC, Jiang DY, Wang LQ. Interventional action of Biejiajian Pill on cellular immune function of tumor-bearing mice with hepatic carcinoma. *Acta Chin Med Pharm* 2012; **40**: 21-23 [DOI: 10.19664/j.cnki.1002-2392.2012.03.007]
- 58 **Wang X**, He YM. Experimental investigation on the antioxidation and immunity in mice with H22 liver cancer by time-selected administration of ginsenoside. *J Wannan Med College* 2012; **31**: 106-108 [DOI: 10.3969/j.issn.1002-0217.2012.02.006]
- 59 **Xiao PY**, Wang ZL, Huang JW. Effects of *Lyciumchinensis* Polysaccharides on tumor suppression and immune function of liver cancer model mice. *Chin Pharm* 2014; **25**: 4046-4048 [DOI: 10.6039/j.issn.1001-0408.2014.43.05]
- 60 **Gan L**. Regulating effect of fructusschisandrae polysaccharide on tumor growth and immune function of H22 vaccination mice. *Immunol J* 2013; **29**: 867-870 [DOI: 10.13431/j.cnki.immunol.j.20130189]
- 61 **Wang XB**, Wang SS, Zhang QF, Liu M, Li HL, Liu Y, Wang JN, Zheng F, Guo LY, Xiang JZ. Inhibition of tetramethylpyrazine on P-gp, MRP2, MRP3 and MRP5 in multidrug resistant human hepatocellular carcinoma cells. *Oncol Rep* 2010; **23**: 211-215 [PMID: 19956884]
- 62 **Gu W**, Liu L, Fang FF, Huang F, Cheng BB, Li B. Reversal effect of bufalin on multidrug resistance in human hepatocellular carcinoma BEL-7402/5-FU cells. *Oncol Rep* 2014; **31**: 216-222 [PMID: 24173654 DOI: 10.3892/or.2013.2817]
- 63 **Liao ZZ**, Wei LM, Xu LY, Liang G. Effect of Hedyoticidiffusa injection in reversing multi-drug resistance of human hepatoma BEL-7402/5-FU cells. *J Xi'an Jiaotong Univ (Med Sci)* 2015; **36**: 554-557
- 64 **Huang XD**, Guo YL, Huang LZ, Zhou Q, Tian XF. Study on the effects and mechanism of hirudo extract on the sensitivity of chemotherapeutic drugs and apoptosis inducing in human hepatoma HepG2 cells. *Chin J Tradit Chin Med Pharm* 2015; **30**: 2094-2096
- 65 **Zhou SF**, Li YF, Liu C, Li M, Yang W. The reverse effect of Qizhu decoction on multidrug-resistant human colorectal carcinoma cell line HCT-8/V and hepatocarcinoma cell line Bel/FU. *Chin J Integr Trad West Med Dig* 2014; **22**: 126-128 [DOI: 10.3969/j.issn.1671-038X.2014.03.04]
- 66 **Zhang XL**, Huang T, Yang XF, Huang L, Li Y. Experimental studies on reversion effects of Shehuang Xiaoliu decoction on multidrug resistance of human hepatoma cells. *Chin J Tradit Med Sci Tech* 2014; **21**: 25-27, 32
- 67 **Ling BF**, Wang RP, Zou X, Hou Q. Impacts of Jianpi Huayu Formula on Bel-7402/5-FU cell surface drug resistance protein in liver cancer. *World J Integr Tradit West Med* 2013; **8**: 120-123 [DOI: 10.13935/j.cnki.sjzx.2013.02.020]
- 68 **Wei Y**, Zhang HY, Liang G. The reverse effect of Quercetin on multidrug resistance of human hepatocellular carcinoma. *Tianjin Med J* 2012; **40**: 1022-1025 [DOI: 10.3969/j.issn.0253-9896.2012.1.0.018]

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