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 chemotherapeutic 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), 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\[3\]. Other herbal medicines used to treat less common symptoms and signs of HCC are also provided in Table 4.

**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\[5\], 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. 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 Ruangpanian 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.
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 decrease in white blood cell and platelet counts of H2 hepatoma transplanted tumor caused by chemotherapy13. Combining Rhizoma Atractylodis Macrocephalae (Baizhu) and Rhizoma Phragmitis (Lugen) reduces the vomiting caused by chemotherapy in H2 hepatoma carcinoma-bearing mice14, 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 (Bayuezha) have also been reported to reduce side effects and improve the efficacy of chemotherapy for HCC in H2 hepatoma bearing mice15-18. 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 patients19. Jianpi Jiedu Formula minimized hepatic dysfunction following transarterial chemoembolization (TACE) treatment in 16 patients20. Similarly, the Zippi Decoction was associated with improved hepatic function following TACE when compared to TACE alone21. Jianpi Li Qi Decoction in 52 patients and Jiedu Granules combined with Cinobufacini in 60 patients alleviated signs and symptoms of the postembolization syndrome following TACE22. Finally, it should be noted that on occasion, TCM can adversely affect patient outcomes when TCM and chemotherapy drugs interact23.

### 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 trifoliate (Thunb.) and Koidz (Sanyemutong) seed extract inhibited the proliferation of various human HCC cell lines via induction of endoplasmic reticulum stress in vitro24 whereas the ethyl acetate extraction from a Chinese herbal formula, Jiedu Xiaozheng Yin inhibited proliferative activity by suppression of the

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

| Category | Herb name                          | Relative frequency |
|----------|------------------------------------|--------------------|
| Herbs that expel wind and damp: | Baizhu, Huangqi, Danqingshi, Shangyao, Baimao, Jisheccao | 27.70% |
|           | Herbs that clear the heat:         | 19.26%             |
|           | Baihuasheshecao, Banzhuzilian, Shengdihuang, Zhizi, Huangqin, Qinghao | 13.67% |
|           | Herbs that invigorate blood and dissolve stasis: Ezhu, Danshen, Yujin, Tubiechong | 12.04% |
|           | Herbs that promote urination and percolate dampness: | 8.39% |
|           | Fuling, Yiyiren, Yinchen, Cheqianzi, Yumixu | 4.14% |
|           | Herbs that rectify qi:             | 3.18% |
|           | Zhiqiao, Chenpi | 2.35% |
|           | Herbs that release the exterior:   | 3.81% |
|           | Chaithu, Guizhi | 2.94% |
|           | Herbs that promote digestion:      | 1.91% |
|           | Jinejüin, Muxian | 1.86% |
|           | Herbs that relieve cough, dissolve phlegm and calm panting: | 0.91% |
|           | Banxia, Tinglizi, Walengzi | 0.46% |
|           | Herbs that stagnate bleeding:      | 0.08% |
|           | Sanqi, Xianhecao, Baimaogen | 0.42% |
|           | Herbs that transform dampness:     | 0.02% |
|           | Houpo | 0.42% |

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### 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 |
|-----------|-------------------|-----------|-------------------|
| Fuling    | 5.20%             | Radix Angelicae Sinensis (Danggui) | 2.33% |
| Rhiiza Atractylodis Macrocephala (Baizhu) | 5.20% | Carapax Trionycis (Bieja) | 2.22% |
| Radix Astragali Mongolici (Huangqi) | 4.07% | Radix Bupleuri Chinensis (Chaihu) | 3.66% |
| Herba Hedystidis (Baihuasheshecao) | 3.75% | Radix Codonopsis (Dangshen) | 3.02% |
| Radix Glycyrrhizae (Gancao) | 3.71% | Radix Paeoniae Alba (Baishao) | 3.03% |

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Xi SY et al. Chinese herbal medicine and HCC

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801 November 27, 2018 | Volume 10 | Issue 11
polycomb gene product Bmi1 and Wnt/β-catenin signaling and inducing G0/G1 phase arrest in vitro and in vivo. Coptis chinensis (Huanglian) restrained HepG2 cell proliferation through activation of the the NAG-1 gene enzyme in vitro. 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, and Chaiqiyigan granula enhanced Taxol-induced growth inhibition of HCC xenografts in nude mice. 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, Compound Recipe Kushen SMMC, which inhibited 7721 cell proliferation in vitro, and Fuzheng Yiliu Granule, which inhibited PLC tumor growth in H22 hepatoma-bearing ICR mice and the HepG2 cell line. 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 SMMC-7721 cells by downregulating p53 gene expression in vitro. TCM matrine, a component of Radix Sophorae Flavescentis (Kushen), induced apoptosis and cell arrest by altering Bel-2, Bax, and miR122a expression in human HepG2 cells and murine HCC cells. 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, Baiaclein, 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 invasion of HCC cells by inhibiting multiple signal transduction pathways including ERK/phosphatidylinositol 3-kinase/Akt upstream of NF-κB 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 adhesiveness 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-D2O 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 intracellular 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 alcefolius Poir (Cuyuxiaouzou) and Livistonachinensis seeds (Pokuizi), 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-β1 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 CD8+\(^{+}\), CD14+\(^{+}\), 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 immuno-modulator 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 CD8+\(^{+}\) and CD4+\(^{+}\)/CD8+\(^{+}\)\(^{55}\). Shaoyao XuanJung Recipe, Biejiajian Pill, Ginsenoside Rg3, Fructus Lycii (Gouqizi) polysaccharide, and Fructus Schisandrae Chinesis (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 Hedyotidiffusa (Baihuasheshecao) injection, achieved the same effect in BEL-7402/5-FU cells\(^{62-63}\), and Hirudo (Shuizhi) extract, Qizhu Decoction, Shehuang Xiaoliu...
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 epidemiology 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.1673-7202.2015.05.003]

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 L, Ni L. [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/cjcmn20120933]

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 Clin Med 2012; 27: 1083-1084 [DOI: 10.16368/j.issn1674-8999.2012.09.006]

7 Li XL, Lan MY, Wu LT, 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.issn1673-7202.2014.10.019]

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; 51: 145-148 [DOI: 10.13463/j.cnki.cejzy.2015.01.050]

12 Lu YX, Lu XQ, Wu FS, Tan ZW, Mo YJ, Lai L. Effect of Qudu
Xi SY et al. Chinese herbal medicine and HCC

Int J Oncol 2013; 42: 202-210 [PMID: 23165653 DOI: 10.3892/ijo.2012.1703]

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: 19726849]

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: 23870190 DOI: 10.1186/1472-6882-13-185]

You M, Luo M, Liao W, Su X, Wu J, Jing L. [Chaiqiyigan granula 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]

Wang CJ, Liu YZ, Xu XM. Influence of JianpiHuai Recipe serum on cell proliferation of human hepatocellular carcinoma Bel-7402. China Clin Rehabil 2006; 10: 82-84

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 [PMID: 10.13463/j.cnki.jjzy.2011.07.049]

Cao ZY, Chen XZ, Liao LM, Peng J, Hu RX, Liu ZZ, Du D. Fuzheng Yiliu Granule improves the growth of hepatocellular cancer via regulating immune function and inducing apoptosis in vivo and in vitro. J Surg Oncol 2011; 17: 691-697 [PMID: 21910071 DOI: 10.1007/s00795-011-8473-3]

Li LH, Pi WX, Cheng HH, 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. Nanning J Tradit Chin Med 2010; 32: 2215-2217 [PMID: 10.13192/j.jlictm.2010.11.140.yehl.064]

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 hepatocyte-specific miR122 in human hepatocellular carcinoma HepG2 cell line. Int J Clin Exp Med 2015; 8: 9004-9012 [PMID: 26309553]

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]

Zhao XL, Xu GC, He LM, Ma L. Apoptosis of human HepG2 cells induced by Gueretin. Pract Cardiovasc Disord 2010; 18: 310-311

Hu B, Du Q, Deng S, An HM, Pan CF, Shen KP, Xu L, Wei MM, Wang SS. Lisigusticum lucidum Ait. fruit extract induces apoptosis and cell senescence in human hepatocellular carcinoma cells through upregulation of p21. Oncol Rep 2014; 30: 1037-1042 [PMID: 25017491 DOI: 10.3892/or.2014.3312]

Hu B, An HM, Shen KP, Xu L, Du Q, Deng S, Wu Y. Modified Yi Guan Jian, a Chinese herbal formula, induces anokias in Bel-402 human hepatocarcinoma cells in vitro. Oncol Rep 2011; 26: 1465-1470 [PMID: 21822542 DOI: 10.3892/or.2011.1414]

Chen T, Hu W, Cui BP, Li JH. Panaxiapjleuvarusin promotes proliferation of H22 cells in mice and its mechanism of action. World J Chin J Digest 2007; 15: 2597-2601

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]

Zhang DM, Liu JS, Deng LJ, Chen MF, Liu A, Cao HH, Tian HY, Fung KP, Kurihara H, Pan JX, Ye WC. Arenoobufagin, 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]

Lin HJ, Kao ST, Siao YM, Yeh CC. The Chinese medicine Sinan inhibits HBs-associated migration and invasiveness of human hepatocellular carcinoma cells. BMC Complement Altern Med 2015;
15: 348 [PMID: 26446078 DOI: 10.1186/s12906-015-0870-6]

Wen B, Sun H, He S, Cheng Y, Jia W, Fan E, Pang J. [Effects of Biejiqian 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: 1755-1762 [PMID: 25379977]

Li LX, Ye SL, Wang YH, Li JS, Sun RX, Xue Q, Chen J, Gao DM, Zhao Y. Inhibiting effect of Jinhong Capsule on high-metastatic human hepatocellular carcinoma cell lines. Chin Hepatol 2011; 16: 240-241 [DOI: 10.14049/j.cnki.issn.1008-1704.2011.03.001]

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

Sun J, Zhou X, Liu Y. [Study on preventive and therapeutic effect of radix salviae miltiorrhizae on recurrence and metastasis of liver cancer]. Zhong Xiu Yi Jie He Za Zhi 1999; 19: 292-295 [PMID: 11783245]

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. Biochem Biophys Acta 2015; 1852: 541-551 [PMID: 25496992 DOI: 10.1016/j.bbadis.2014.12.004]

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: 25333345 DOI: 10.3892/mmr.2014.2702]

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: 10.3829/ or.2014.3051]

Sun ZJ, Yu HB, Zhang Y, Liu XG, Du LX. The effects of Resveratrol on growth and angiogenesis of HepG2 tumor model in vivo. Shauan Med J 2010; 39: 279-281

Wang M, Zhang X, Xiong X, Yang Z, Sun Y, Yang Z, Hoffman RM, Liu Y. Efficacy of the Chinese traditional medicinal herb Celastrius orbiculatus Thunb on human hepatocellular carcinoma in an orthotopic fluorescent nude mouse model. Anticancer Res 2012; 32: 1213-1220 [PMID: 22493351]

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.zzyl.2005.01.014]

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 Travel Med 2015; 13: 100 [PMID: 25889022 DOI: 10.1186/s12967-015-0465-5]

Xu DJ, Chen MZ. Antitumor activity of APS and its mechanism of action. Chin Hosp Pharm J 2005; 25: 923-925

Chen XZ, Cao ZY, Yang JL, Du J. Effects of Chinese medicine compound recipe on apoptosis and immune function of subcutaneous transplanted tumor with H22hepatocarcinoma. Fujian J Tradit Chin Med 2009; 40: 52-54 [DOI: 10.13260/j.cnki.jftc- cm.009689]

Sun Y, Zhang AQ, Gao FY. Immune effect of Shaoxyao 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]

Luo QD, Wang YH, Zhao HY, Wang B, Du FX, Deng FC, Jiang DY, Wang LQ. Interventional action of Biejiqian 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]

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]

Xiao PY, Wang ZL, Huang JW. Effects of Lyciumchinensis Polysaccharides on tumor suppression and immune function of liver cancer model mice. Chin Pharm 2010; 25: 4046-4048 [DOI: 10.6039/j.issn.1001-0408.2014.03.05]

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]

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]

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]

Liao ZZ, Wei LM, Xu LY, Liang G. Effect of Hedyotidisflusa 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

Huang XD, Guo YL, Huang LZ, Zhou Q, Tian XF. Study on the effects and mechanism of hirudo extract on the sensitivity of chemo-therapeutical drugs and apoptosis inducing in human hepatoma HepG2 cells. Chin J Tradit Chin Med Pharm 2015; 30: 2094-2096

Zhou SF, Li YF, Liu C, Li M, Yang W. The reverse effect of Quzhou 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]

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

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 Med West Dig 2013; 8: 120-123 [DOI: 10.13935/j.cnki.sjxgz.2013.02.020]

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.0253-9896.2012.1.018]

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