Cancer Reports and Reviews

Review Article ISSN: 2513-9290

Traditional Chinese medicine combined with other therapies for treatment of hepatocellular carcinoma in clinical trials

Shuying Feng[1,2], Man Zhu[1], Shu Hu[1], Zhengshun Xu[1], Aifang Li[1] and Changyu Sun[2*]

[1]Medical College of Henan University of Science and Technology, Luoyang, Henan 471023, China

[2]Infectious Disease Department of First Affiliated Hospital, Zhengzhou University, Zhengzhou, Henan 450052, China

Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors worldwide with a high mortality, and still there are only few effective methods to treat it. To this end, alternative medicines from traditional Chinese medicine (TCM) are being investigated for their ability to eliminate the tumor or halt its progression. A large number of studies have shown that TCM can be an effective approach to treat the HCC in clinical trials when used alone or in combination with other therapies. Thus, TCM has made significant progress, and has begun to gain worldwide popularity for promoting healthcare and HCC treatment. Because of this progress, periodic summaries are needed to facilitate further research for the use of TCM to treat HCC. This paper provides a comprehensive summary of this work with regard to the following aspects: herbalist views on the etiology and therapeutic principles for treatment of HCC, treating HCC by TCM alone, treating HCC with TCM in combination with resection, chemotherapy, radiotherapy and interventional therapy, and other therapies. Additionally, the current main problems and future application prospects for treatment of HCC by TCM described, which could provide scientific guidance for clinician as well as references for the treatment of other cancers.

Abbreviations: ALB: Albumin; ALT: Alanine transaminase; AST: Aspartate aminotransferase; CI: Confidence interval; DBIL: Direct bilirubin; DFS: Disease-free survival; GGTP: Gamma glutamyl transpeptidase; HCC: Hepatocellular carcinoma; IC: Intraperitoneal chemotherapeutics; ICGR15: Retention rate of indocyanine green at 15 Minutes; KPS: Karnofsky score; MST: Mean survival time; NK: Natural kill cell; OPN: Osteopontin; OS: Overall survival; PFS: Progression-free survival; PRIT: Pain-relieving initial time; PRST: Pain-relieving sustained time; QOL: Quality of life; RECIST: Response evaluation criteria in solid tumors; RFA: Radio-frequency ablation; RR: Relative risk; SR: Survival rate; TACE: Transcather arterial chemoembolization; TBIL: Total bilirubin; TCM: Traditional Chinese medicine; WBC: White blood cell; WM: Western medicine

Introduction

Hepatocellular carcinoma (HCC) is a lethal malignant tumor worldwide that has a high morbidity and mortality. According to statistics, it is the fifth most commonly diagnosed cancer and the second most common cause of cancer death in men, and the seventh most commonly diagnosed cancer and the sixth leading cause of cancer death in women [1]. Many factors can lead to HCC, such as water and food pollution, hepatitis B and C infection, extensive drinking and smoking, and so on [2-6], causing an increase in the morbidity and mortality due to HCC every year. Additionally, early-stage diagnosis of HCC is extremely difficult and its prognosis is poor. All these factors make it a serious threat to human health. Thus, an effective approach for treating HCC is very necessary and must be developed.

The current methods for treating HCC include liver resection, chemotherapy, radiotherapy, liver transplant, and other therapies [7]. While these methods can have a positive effect, they are far from satisfactory. The main reasons are largely due to the deficiency of effective drugs, tumor multidrug resistance, and the multistage process and high recurrence rate of HCC. So, an increasing number of investigators and oncologists are seeking other means and medicines to treat the HCC. Because traditional Chinese medicine (TCM) has unique features, it has received a surge of interest and has been extensively adopted to treat HCC patients in clinical works [8]. Up to date, a large number of clinical trials show that TCM treatment of liver cancer is feasible and its efficacy is definite [9-12]. This paper is to give a comprehensive summary for TCM treatments of HCC to provide detailed background information to clinicians. Moreover, the current main problems in this area of research and future application prospects for using TCM to treat HCC with TCM are extensively described.

Herbalist's views on the etiology and therapeutic principles of HCC

To date, there are many records about the symptoms consistent with HCC in ancient Chinese literature. For example, the ancient Chinese medical book 'Nei Jing', in which the liver-related symptoms were described as the 'Fei qi', 'Gu zhang', 'Xie tong', 'Fu liang', and 'Huang dan' etc. Additional symptoms consistent with HCC recorded

Correspondence to: Changyu Sun, Infectious Disease Department, First Affiliated Hospital of Zhengzhou University, No. 1 East Road of Construction, Zhengzhou, Henan 450052, China, Tel: 8613673665207; E-mail: changyu8188@163.com

Key words: *traditional Chinese medicine, hepatocellular carcinoma, recent progress, clinical trial, current problems*

Received: July 20, 2017; **Accepted:** August 11, 2017; **Published:** August 14, 2017

as 'Ji ju' and 'Zheng jia' are found in Miraculous Pivot and Synopsis of Golden Chamber, respectively. Some ancient Chinese medical books also describe the etiology for these symptoms. For instance, 'Required Readings for Medical Professions' describes the deficiency energy of body and the detention of pathogenic factors, which are consistent with the etiology of HCC. The ancient book 'Miraculous Pivot' considers that moodiness is an important factor of HCC development. Based on ancient literature and clinical experience, herbalists have their own understanding about the etiology of HCC. Some herbalists viewed that deficiency of Qi and detention of pathogenic factors can cause cementation of Qi stagnation, blood and phlegm stasis, finally resulting in the development of HCC. Some herbalists considered that phlegm and Qi stagnation, and noxious heat with blood stasis, which resulted from the weakness of stomach and spleen and damage of diet, as eventually leading to the occurrence of HCC. Except that, other herbalists suggest that many factors, such as hot and humid invasion, emotional disorder, and physical weakness in the elderly, contribute to the occurrence of HCC. Given this, it is a clear fact that the interaction of internal factors together with external factors, contribute to the occurrence of HCC [13,14].

As to the therapeutic treatment of HCC, most herbalists assert that invigorating Qi, regulating Qi-flow, activating blood circulation, nourishing Yin and detoxification play major roles in the treatment of HCC [15,16]. Following these methods, TCM can promote appetite, dissipate blood stasis, and remove toxins, which results in the inhibition of tumor growth [17]. Identification of the type of HCC syndrome involved is also important for the application of the most effective TCM treatment. For example, replenishing vital energy for Qi deficiency syndrome, replenishing blood for blood deficiency syndrome, nourishing Yin for Yin deficiency syndrome, eliminating moisture for water-dampness syndrome, and soothing the liver and regulating energy for Qi stagnation syndrome [18-20]. Therefore, identifying the correct HCC syndrome helps clinicians make effective individualized strategies, and also achieves a better therapeutic effect over other medicines. However, currently, the clinicians' experience and lack of standard and uniform therapeutic methods make the current clinical application of TCM fall far behind the application of Western medicine (WM) therapeutic methods.

Treatment of HCC using TCM alone or in combination with other supportive therapeutic methods

So far, a large number of effective TCM methods have been developed through long term clinical practice and experience. The most common methods are based on the therapeutic principles of regulating Qi-flow, invigorating Qi, activating blood circulation, clearing heat, removing dampness, and nourishing Yin [15]. Under the direction of this principle, TCM not only significantly inhibits tumor growth preventing progress of the disease [21,22], but also improves the survival time and overall survival (OS) rate of patients [23,24] (Table 1). Through the protection of liver function and regulation of body immunity, TCM can also improve the patient's quality of life (QOL) and reduce adverse reactions [25,26]. In some cases, if long-term using TCM treatment, HCC could be completely regressed and the patient remains alive longer than 31 months after relapse [27]. Additionally, hepatic fibrosis, cirrhosis and rate of HCC occurrence in patients have been significantly inhibited [28,29]. Further, TCM has a good analgesic effect, and can promote the restoration of bowel peristalsis and minimize abdominal distension and urinary retention [30,31]. A series of statistical analyses showed that 8 herbs are closely associated with tumor proliferation, metastasis, angiogenesis and apoptosis [32]. These analyses also demonstrated that the products containing Ginseng, *Astragalus* and *Mylabris* have the greater significant therapeutic effects on HCC [33]. Therefore, from these analyses can be inferred that TCM is an independent favorable factor for the treatment of HCC.

In addition to oral route, TCM can also be used for external treatment, such as topical scrubbing and fumigation. Through external application, TCM can be absorbed directly through the skin which reduces the burden of liver metabolism and gastrointestinal reaction, and also overcomes the problem the insufficient efficacy by being excluded [34]. Frequently, TCM are combined with conventional WM to treat HCC, which involves treatment to protect the liver, nutrition therapy, and treatment of other clinical symptoms. Because the cost of the combination therapy (WM with TCM) is low and the therapeutic effect is better, it is well accepted by patients [9,26]. However, these few reports describe very promising results, as just summarized, and these results warrant further large-scale experiments. To obtain the better curative effect, new TCM formulas have been explored using animal experiments [35,36]. Through regulation of different signal pathways associated with autophagy [37], apoptosis [38], angiogenesis [39], cell proliferation and cell cycle [40], TCM could considerably suppress HCC growth in nude mice. In addition, some TCMs could effectively inhibit tumor invasion and metastasis [41,42], extended the animal survival time and cumulative survival rate (SR), lessened the weight loss rate in the mice [43,44], and enhanced the production of serum cytokines and other indexes [45]. Based on these studies, it is easy to see that the combined TCM/WM treatment of HCC is an important research direction. However, it is also important in these investigations to pay careful attention to avoid the occurrence of negative effects from various combined treatment methods [46].

TCM combined with other therapies for treatment of HCC

As mentioned above, although the application of TCM alone has played a definite role in the treatment of liver cancer, its main application is in combination with other therapies. Up to date, there are many available combination therapies for the treatment of HCC, such as the combination of TCM with resection, chemotherapy, radiotherapy, interventional treatment, and other methods (Table 2). In the following section, the combination of TCM with various other therapies will each be described.

Combination of TCM and resection for treatment of HCC

Resection is an effective method to treat HCC, especially to early HCC [47]. But due to the low immunity and liver failure after resection, it has a poor long-term effect and with a high recurrence of tumor growth as well as metastasis. So, it has not been generally accepted as a method to treat HCC patients [48]. Resection combined with TCM is a good choice of therapy to overcome these deficiencies. Through combined with resection, TCM can modulate immunity, balance the entire body, and dramatically improve the patient's liver function and OS [49,50]. In addition, the combined therapy prolonged the progression-free survival (PFS) and disease-free survival (DFS), and reduced post-operative recurrence and metastasis [51,52], and shorten the patient's hospital stay and reduce the incidence of postoperative ileus in patients with liver cancer [53,54]. Based on the benefits of this combination therapy, clinicians have used other therapies in combination with TCM to treat HCC with purpose of achieving a better curative effect. These results support conducting some large-scaled, randomized control trails to provide a greater level of data by which this combination therapy can be evaluated and utilized.

Combination of TCM and chemotherapy for treatment of HCC

Chemotherapy is one of the most conventional therapeutic ways to treat malignant cancers. Due to obvious negative side effects and easily drug resistance, chemotherapy is seriously limited in the treatment of many cancers. Through clinical application of TCM combined with chemotherapy, the results indicated that the addition of TCM relieved the adverse reactions of chemotherapy, such as pain, nausea and vomiting, and also improved the survival time and the quality of life of patients [55,56]. However, due to the limited number of these studies, these findings should be further confirmed through high-quality and rigorously controlled trials. To deeply improve efficacy and reduce the side effects of chemotherapy, intraperitoneal chemotherapeutics (IC)

Table 1. Treatment of HCC by TCM alone or in combination with the supportive therapy

TCM formula names	Effects		References
	Control group	TCM treatment group	
Different Chinese medicines	12 months MST, 48.4% 1-year SR, 26.6% 2-year SR	36 months MST, 76.7% 1-year SR, 56.1% 2-year SR	Man et al. (2015)
TCM prescription	13.4% 1-year SR	32.5% 1-year SR	Qiu et al. (1988)
Gan kang 6	9.76% tumor effective rate, 26.83% symptoms effective rate	18.29% tumor effective rate, 81.71% symptoms effective rate	Zhang et al. (2012)
Cinobufacini injection	32% progressive rate, 18% SR of >12 months, serum total bilirubin and ALT increased a lot	18% progressive rate, 30% SR of >12 months, serum total bilirubin and ALT decreased obviously	Chen et al. (2003)
Ganji decoction and Ailitong	5.3 months MST, 7.78±1.95 h PRST, 42.5% 0.5- year SR, 18.1% 1-year SR	8.9 months MST, 10.37±2.18 h PRST, 65.9% 0.5-year SR, 38.6% 1-year SR	Tian et al. (2010)
Sho-saiko-to	34% cumulative incidence, 60% survival curve	23% cumulative incidence, 76% survival curve	Oka et al. (1995)
Xiaoaiping injection	24.5 weeks MST, 15 weeks PFS, 25.0% cumulative SR of 6-months	27.0 weeks MST, 18 weeks PFS, 33.3% cumulative SR of 6-months	Huang et al. (2013)
Different TCM	6 months MST, 0% 5-year OS rate	13 months MST, 2.61% 5-year OS rate	Gao et al. (2016)
Qu tong ling	4.81±2.21h PRST	6.42±1.24h PRST	Li et al. (1996)
Jia Wei Si Jun Zi Tang	ICGR15 18.36%±9.82% before second treatment, 19.12%±9.96% after second treatment	ICGR15 12.18%±5.22% before second treatment, 12.83%±5.28% after second treatment	Zhang et al. (2004)

Table 2. Treatment of HCC by the combined therapy of TCM and other methods

TCM combined methods	TCM formula names	Effects		References
		Combined method alone	Combination therapy	
Hepatectomy	Ruanjianhugan tablets	20.77 months median OS, 5-, 10-year OS rate was 13.84% and 13.84% respectively	151.20 months median OS, 5-, 10-, and 15-year OS rate was 83.94%, 45.50% and 71.22% respectively	Sun et al. (2012)
	Ruanjianhugan tablets (Invention after resection)	43.87 months median OS, 5-, 10-, and 15-year OS was 33.34%, 55.58% and 9.26% respectively		
	Chinese herbal medicine	All these indexes lower than Chinese herbal medicine group	Hepatic function indexes were improved significantly	Xu et al. (2001)
	Jianpi Huayu	22.6 months median DFS, 49.8 months median survival, 1-, 3- and 5-year DFS rate was 75.0%, 23.3% and 6.4% respectively, 1-, 3- and 5-year OS rate was 96.7%, 74.7% and 37.4% respectively	28.7 months median DFS, 52.6 months median survival, 1-, 3- and 5-year DFS rate was 78.2%, 29.2% and 14.3% respectively, 1-, 3-, and 5-year OS rate was 98.3%, 78.0% and 43.6% respectively	Zhong et al. (2014)
	Simo decoction	16.5d hospital stay, 29.6h first peristalsis	14.0d hospital stay,19.6h first peristalsis	You et al. (2015)
	Jiedu xiaozheng yin, Fuzheng yiliu recipe	30.0% accumulative 3-year SR, 80.0% 2-year recurrence rate	45.5% accumulative 3-year SR, 54.8% 2-year recurrence rate	Chen et al. (2005)
Chemotherapy	Shen-Ling-Bai-Zhu	Tumor sizes were decreased -52%	Tumor sizes were decreased -58%	Xi et al. (2016)
	Chinese herbal medicine	No these functions	Improved survival at 12 months (RR, 1.55; 95% CI, 1.39-1.72), 24 months (RR, 2.15; 95% CI, 1.75-2.64), and 36 months (RR, 2.76; 95% CI, 1.95-3.91), tumor response increased	Shu et al. (2005)
	Yanshu injection	45.2% remission rate, 40.5% 1-year SR, 82.6% pain relief rate, 66.3% effective rate of improved QOL	60.5% remission rate, 51.2% 1-year SR, 95.8% pain relief rate, 82.8% effective rate of improved QOL	Guan et al. (2006)
	Xiaoshui decoction	21.4% short-term total effective rate, 10.87±7.76 days interval of aspirating ascites, 14.3% 1-year SR	42.4% short-term total effective rate, 17.95±9.63 days interval of aspirating ascites, 33.3% 1-year SR	Wu et al. (2005)
Radiotherapy	Xuefu Zhuyu decoction	No these functions	1-, 3- and 5-year SR were higher than those of the control group by 20.0%, 23.4% and 16.6% respectively, enhance the radiosensitivity of liver cancer cells and the radiation tolerance of normal hepatocytes, reduce the side effect of radiotherapy	Han et al. (1997)
	Jian Pi Li Qi group	1-, 3- and 5-year SR was 45.77%±6.34%, 26.06% ±6.85% and 14.48%±7.19% respectively, 11.1 months MST	1-, 3- and 5-year SR was 86.67%±3.58%, 55.25% ±6.59% and 42.97%±11.98% respectively, 53.4 months MST	Yu et al. (1992)

TACE	Jian Pi Li Qi	12 PES increased significantly after TACE	7 PES relieved significantly, liver function improved	Xu et al. (2016)
	Jianpi Ligan	80% treatment success rate, 26% 3-year OS probability	96.2% treatment success rate, 37.7% 3-year OS probability, reduction of side effects, improvement of long-term viability	Tang et al. (2016)
	Jianpi Huoxue group	ICGR15 16.64%±10.15% before second treatment, 19.80%±11.26% after second treatment	ICGR15 11.69%±5.13% before second treatment, 11.53%±5.30% after second treatment	Chen et al. (2002)
	Cinobufacini injection	23.1% objective response rate	53.6% objective response rate, less adverse events	Dong et al. (2016)
	Asparagus polysaccharide or gum	No these functions	Liver tumor growth and angiogenesis were significantly inhibited, immunomodulatory functions were improved	Weng et al. (2014)
	Gan'ai No. I and No. II	0.5-, 1- and 2-year SR was 50.0%, 33.3% and 16.7% respectively, 1- and 2-year recurrence rate was 66.7% and 90.0% respectively	0.5-, 1- and 2-year SR was 76.7%, 56.7% and 30.0% respectively, 1- and 2-year recurrence rate was 43.3% and 66.7% respectively	Shao et al. (2001)
	Cantharidins	Lower overall efficient rate and KPS	Higher overall efficient rate and KPS, lower WBC count, relieving side effects and improving the QOL	Zhang et al. (2014)
	Jinlong capsule	40% clinical efficacy, 69.86±11.58 KPS, 151.09±83.90 OPN	60.38% clinical efficacy, 84.35±12.19 KPS, 117.69 ±78.50 OPN	Wu et al. (2010)
	JDF granule preparation	5.87 months MST, 1-, 2-, and 3-year SR was 26.9%, 12.6% and 2.4% respectively	9.2 months MST, 1-, 2-, and 3-year SR was 41.2%, 18.4%, and 9.6% respectively	Yu et al. (2009)
	Shentao Ruangan pill, hydroxycamptothecine	262 days MST, 0.5-, 1- and 2- year SR was 64.29%, 25.00% and 8.33% respectively	326 days MST, 0.5-, 1- and 2- year SR was 80.95%, 41.39% and 12.42% respectively	Lin et al. (2005)
	Jiedu granules, Cinobufacini injection (TACE+Resection)	8.03 months PFS, 39.90 months MST, 1-, 2-, 3-, 4- and 5-year PFS rate was 34%, 11%, 7%, 2% and 0% respectively, 1-, 2-, 3-, 4- and 5-year SR was 79%, 70%, 60%, 60% and 36% respectively	18.07 months PFS, 49.53 months MST, 1-, 2-, 3-, 4- and 5-year PFS rate was 61%, 39%, 26%, 22% and 12% respectively, 1-, 2-, 3-, 4- and 5-year SR was 90%, 82%, 80%, 70% and 63% respectively	Chen et al. (2012)
	Cinobufacini injection and Jiedu granule	34.49 months median recurrence-free survival, recurrence rate of 1, 2 and 3 years was 28.8%, 42.5% and 54.0% respectively	46.89 months median recurrence-free survival, recurrence rate of 1, 2 and 3 years were 17.7%, 33.0% and 43.5% respectively	Chen et al. (2012)
	Ginsenosides	No these functions	lower the median time of symptoms persistence, alleviate the side effects and bone marrow inhibition of chemotherapy	Feng et al. (2005)
Hepatic arterial infusion	Curcuma aromatic oil, Chemical drugs	31.25% total effective rate, 6 months MST, 1-, 2- and 3-year SR was15.6%, 3.2% and 0 respectively	43.75% total effective rate, 10 months MST, 1-, 2- and 3-year SR was 37.5%, 13.3% and 6.9% respectively	Cheng et al. (2001)
Radiofrequency ablation	Aidi injection	55.0% relapse rate of tumor	20.0% relapse rate of tumor	Lou et al. (2007)
Microwave coagulation	Shenqi mixture	55.56% effective rate, 12-month, 18-month, 24-month SR was 66.77%, 55.56%, 41.67% and the reoccurrence rate was 27.28%, 47.22%, 69.44% respectively	75.00% effective rate, 12-month, 18-month, 24-month SR was 83.33%, 77.78%, 55.56%, and the reoccurrence rate was 13.89%, 22.22%, 41.67% respectively	Lin et al. (2005)
Microwave ablation	Fuzheng Yiliu recipe	28. 19±6.59 $CD4^+$ level, 1.22±0.31 $CD4^+/CD8^+$ ratio, 33.3% tubercle recurrence rate	40.38±12.47 $CD4^+$ level, 1.49±0.41 $CD4^+/CD8^+$ ratio, 14.0% tubercle recurrence rate	Zhao et al. (2012)
Invention therapy	Oleum *Fructus Bruceas,* Ganji decoction, Ailitong	3.73±1.52h PRIT, 7.78+/-1.95h PRST, 5.3 months MST, 0.5- and 1-year SR was 42.5% and 18.1% respectively	3.77±1.93h PRIT, 10.37+/-2.18h PRST, 8.9 months MST, 0.5- and 1-year SR was 65.9% and 38.6% respectively	Lee et al. (2011)
Invention therapy	Ganji recipe, *Fructus Bruceae* oil emulsion	lower KPS, 5.3 months MST, 0.5- and 1-year SR was 42.4% and 16.1% respectively	higher KPS, 8.9 months MST, 0.5- and 1-year SR was 67.6% and 38.2% respectively, QOL improved	Wang et al. (2009)

has been adopted in the clinical treatment of HCC. IC allow drugs to reach carcinoma nests with increased dosage directly and achieved a resulting in a better result [57]. Combination therapy of the IC and TCM not only enhanced the protection of liver function and the anti-tumor activity [12,58], but also protected the liver from damage induced by IC [57,59]. What's exciting is that some TCM or herbal components, such as andrographolide niosomes [60] and polypeptides in bee venom [61], have significant potential for targeting the liver, which would be very useful for chemotherapeutic treatment of HCC. Therefore, increasing the investigations of these herbs in combination with chemotherapy may be an effective way to quickly develop new chemical drugs for HCC patients.

Combination of TCM and radiotherapy for treatment of HCC

Hepatectomy and chemotherapy are effective treatments for patients with early HCC, but they are not suitable for all patients with liver cancer. For patients who are not suitable for resection or chemotherapy, radiotherapy is a common effective method; this involves delivering radioisotopes through either a percutaneous or transarterial approach in order to reach the nidus and obtain high tumoricidal activity [62,63]. However, hepatoma cells generally have a lower sensitivity to radioisotopes than other cell types that leads to unsatisfactory curative effects [64]. Radiotherapy also often causes

some adverse reactions, such as fever, nausea, chills, poor appetite, and tiredness [65,66]. Clinicians began to investigate the combination therapy of using TCM with radiotherapy to overcome the above adverse effects. Through clinical practice, combining TCM with radiotherapy increased the radiosensitivity of liver cancer cells and the radiation tolerance of normal hepatocytes, and reduced the side effects of radiotherapy [67]. Previous works showed that the curative effect of radiotherapy depends on the tumor cell radiosensitivity to tumor size, or volume, ratio [68]. If treated with the higher mid-plane tissue irradiation dose, patients had a longer survival time after radiotherapy. However, despite TCM mediating the side effects of radiotherapy significantly, it did not have a noticeable anti-tumor effect in the patients. In view of this result, future work to screen a highly effective TCM or combination of TCM and radiotherapy is needed. Further investigation is also needed since, in some clinical trials, there are flaws in the methodological quality and a bias risk in the data.

Combination of TCM and interventional therapy for treatment of HCC

Combined application of TCM and TACE: Compared with the above methods, interventional therapy has the characteristics of rapid drug action and rare or mild side effects, making the HCC patients more willing to accept this method of treatment. So far, the methods of interventional therapies for treatment of HCC are transcather arterial chemoembolization (TACE), percutaneous ethanol injection, microwave ablation, radiofrequency ablation, and others [69]. Among them, TACE is the most commonly used method for patients with HCC, and it used as the standard care for the intermediate and advanced liver cancer patients. However, TACE has also has some dissatisfactory aspects in clinical practice, like TACE itself can't kill cancer cells and often causes serious adverse reactions [70]. Clinicians are investigating combining TCM with TACE to overcome the deficiencies of using TACE alone. As summarized in Table 2, TCM combined with TACE is an effective therapy for HCC patients, and achieves a wide range of therapeutic effects. Firstly, TCM effectively relieves characteristic postembolization syndromes and hepatic functional reserve injury that can occur after TACE [71-73]. TCM can also alleviate the adverse reaction of combined chemotherapeutic agents and promote the recovery of liver function in patients [74,75]. Secondly, TCM can significantly inhibit liver tumor growth and angiogenesis [76,77], while restraining the progress of liver cancer [78,79]. Thirdly, TCM can promote the immune response and improve the QOL of the patient by protecting life functions [74,80], and then prolong survival of patients and improve the prognosis of patients with unrespectable HCC [70,81-83]. Thus, the local application of TCM combined with systemic therapy might be an effective measure of non-operational therapy for treating HCC [11,84]. Finally, TCM can postpone tumor recurrence and metastasis and prolong the recurrence-free survival time of post-surgical patients with HCC [85,86]. In some cases, some TCM have the ability to reduce myelosuppression, and others possess immunomodulatory functions with little toxicity to the host [87,88]. Therefore, exploring new combinations of TCM with TACE is a necessary area of investigation for the clinical treatment of HCC. Future work needs to be done using large samples with random controls.

Combined application of TCM and other interventional therapies: Except for TACE, TCM combined with other interventional therapies have been used to treat HCC, such as radiofrequency ablation, microwave coagulation, argon-helium knife, percutaneous ethanol injection, and others. Radiofrequency ablation (RFA) has gained a wide acceptance as a viable alternative to surgical resection for small HCC because of its comparable long-term survival, reduced morbidity, and greater preservation of hepatic parenchyma. However, RFA is still limited in treating large tumors and some tumors in high-risk locations. In order to compensate for these shortcomings, the use of TCM in combination with RFA has become the target of choice [89]. Using extra herbal medicines in combination with cool-tip RFA could improve immune function and reduce the relapse rate in patients with primary liver cancer [90]. Microwave coagulation is an effective therapy for patients with middle-advanced HCC who have lost the chance of surgical operation. In combination with TCM, microwave coagulation could kill the residue tumor cells thereby preventing the recurrence of liver cancer, and also improve the liver function and enhance cellular immunity [91,92]. Due to the high thermal efficiency and faster ablation time, microwave coagulation is especially suitable for small HCC and tumors located at hepatic dome. At the same time, larger HCC can also be completely ablated by using more effective antenna or simultaneous application of multiple antennae [93]. Additionally, TCM combined with argon-helium knife [94] and percutaneous ethanol injection [95] have been reported occasionally in China. The results showed that with both, TCM had a positive effect in the treatment of HCC. Although direct use of TCM by hepatic artery perfusion/embolization has a good effect [96,97], multimodal treatment strategy, such as RFA + TACE [98], radiofrequency ablation + TACE + hepatectomy [99], TCM+ WM+ intervention [100], is more effective than that of interventional therapy alone for patients. Additionally, multimodal treatment can be used as a helpful bridging therapy for patients who are waiting for liver transplantation. However, there are few studies in this field at present. The combination of TCM with other ablation techniques, such as the laser-induced thermotherapy and high-intensity focused ultrasound ablation, should be developed with the purpose of achieving better therapeutic effects for HCC patients.

Current problems and future application prospects of TCM treating HCC

Collectively, either application of TCM alone or TCM combined with other therapies, have positive therapeutic effects on HCC. However, TCM treatment methods of HCC have some inherent disadvantages, such as the unobvious effect of some herbal medicines, unclear active ingredients of TCM, lack of treatment evaluation standards, and so on [101]. Therefore, below, we summarize the current problems and deficiencies in this field for the purpose of supplying guidance for the clinician to provide scientific medical treatments for HCC. Possible future TCM application prospects for the clinical treatment of HCC and other cancers are also discussed.

Establishing the standard therapeutic program and evaluation system of TCM

In most case, clinicians make individualized treatment strategies according to the ZHENG (mean syndrome) of patients in the clinical practice [85]. Most therapeutic principles are based on the clinical experience, which lacks theoretical basis and causes TCM treatment to give different and, therefore, controversial, results. Additionally, there are no effective criteria to evaluate the effects of TCM, which cause inconsistent conclusions regarding the effect of TCM treatment for HCC. Currently, clinicians often use the Response Evaluation Criteria in Solid Tumors (RECIST) to evaluate the effects of TCM treatment. Although RECIST measures the effect according to the inhibition rate of tumor size, it overlooks anatomic tumor response metrics, the immunity and QOL of patients, as well as the survival time of the tumor [102]. Two possible approaches to address these problems are as

follows: On the one hand, a standard therapeutic program should be established through summarizing the syndrome factors, evolution law of syndromes, and the law of medicine application [103]. On the other hand, according to the theory of syndrome differentiation in TCM, a new evaluation system of TCM should be made in which the PFS, OS, Karnofsky score (KPS) and other factors are included [104]. After establishment of these systems, they will promote the wide application of TCM and have a good value in the prevention and treatment of other cancers.

In depth studies of the mechanism of TCM and isolation of its active ingredient

The anticancer mechanism of some herbal formulas and extracts have been elucidated. In general, the mechanism of anticancer agents is mainly due to the expression specific genes and of specific proteins and regulation of signaling pathways. Specific proteins are mainly the cyclins (D and E) and specific genes include the gene family (Bcl-2 and Bel-2). Through increasing the expression of cyclin D and E and downregulation of the Bcl-2 gene family, TCM has the effect of suppressing cancer cells growth which eventually leads to the inhibition of HCC [105]. Among the regulation of signaling pathways, inducing cancer cell apoptosis and the mitochondrial apoptotic pathway obviously play the important role in the treating HCC with TCM [106]. Although TCM treatment of cancers have a long history in China, most of TCM mechanisms are still unknown. Moreover, a large number of active compounds in TCM have been isolated and their roles have been revealed. For instance, some active ingredients are active against HCC by inhibiting the proliferation and halting the angiogenesis and metastasis of HCC [107-110], or reverse the multi-drug resistance of hepatoma cells resulting in the killing of these cells [22,111]. Although recent studies have found that some ingredients with high anticancer activity have been isolated [112-116], most of them focus only on the HCC cell level, and haven't been used in clinical therapies [117]. Therefore, strengthening the clinical application and the further study of active components in TCM will be of great value for the development of future TCM application.

Developing new TCM formulas and TCM preparations for HCC treatment

As the use of TCM for the treatment of HCC has a long history which has accumulated a large number of TCM formulas and preparations. Compared with WM, TCM has the disadvantages of a slow effect and is vulnerable to personal factors and lifestyles. Thus, TCM prescriptions have always been in the process of improving and developing. In recent years, some new TCM formulas have been developed that can significantly inhibit the survival of liver cancer cells, induce the anoikis in cancer cells, and then inhibit the growth of HCC, such as Huang-lian-jie-du-tang [118], modified Yi Guan Jian [119], Xiaochaihu Decoction [120] and Songyou Yin [121] etc. However, these formulas and preparations are only based on the level of cell research or animal experiments. Thus, it is urgent to strengthen the clinical application of these formulas and preparations with a hope of getting the best anticancer effect. Moreover, the isolation, identification, and modification of the TCM active ingredient is necessary to discover new TCM compounds [122,123]. Additionally, strengthening the study of combined therapies of TCM with other medicines or measures is also an effective strategy to obtain better therapeutic effects. Through the combination therapy, the best drug combination or concomitant medications can be identified that could be widely used in clinical treatment of HCC.

Exploring the new therapeutic modalities of TCM for treatment of HCC

To improve the curative effect of TCM, except the traditional oral route, new administration methods of TCM should be investigated and developed; e.g., intraperitoneal administration [124], intranasal administration [125]. In addition, improving the bioavailability can be regarded as another way to promote the therapeutic effect of TCM. For instance, some adjuvants could increase the solubility of hydrophobic drugs and then improve the therapeutic effect of TCM for HCC [126]. Simultaneously, many studies showed that application of new drug delivery systems is a good way to improve bioavailability, such as a self-micro-emulsifying drug delivery system [127], a single-walled carbon nanotubes delivery system [128], spray congealing technology [129], a nanoparticle drug delivery system [130], and a polymeric delivery system [131]. Hence, development of new drug delivery systems will be the most important therapeutic modalities for the future treatment of HCC. This, together with combining of TCM with other methods to treat HCC, such as the adoptive immunotherapy, targeted therapy, which may be open up new path should be the focus of future research to treat HCC with greater effectiveness.

Conclusion

In summary, regardless of used alone or in combination with other therapies, TCM has the positive therapeutic effects on HCC. Although current there are some problems in the treatment of HCC by TCM, but TCM as an effective approach to treat the HCC in clinical trials is affirmative. Treating HCC with TCM could provide scientific guidance for clinician in the actual practices with the purpose of achieving the better efficacy. Simultaneously, TCM has a bright application prospects for the treatment of HCC, and also could be widely promote in the treatment of a variety of other cancers.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. U1304805), the Key Research Project of Science and Technology Department of Henan Province, China (No.152102310045), and the Student Research Training Program of Henan University of Science and Technology, China (No. 2015112). The authors gratefully acknowledge Prof. Russell Carlson of Department of Biochemistry & Molecular Biology of University of Georgia for modifying and polishing this manuscript.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, et al. (2011) Global cancer statistics. *CA Cancer J Clin* 61: 69-90. [Crossref]

2. Chen W, Zheng R, Zhang S, Zhao P, Zeng H, et al. (2014) Annual report on status of cancer in China, 2010. *Chin J Cancer Res* 26: 48-58. [Crossref]

3. Tatsumi A, Maekawa S, Sato M, Komatsu N, Miura M, et al. (2015) Liver stiffness measurement for risk assessment of hepatocellular carcinoma. *Hepatol Res* 45: 523-532. [Crossref]

4. Franceschi S, Raza SA (2009) Epidemiology and prevention of hepatocellular carcinoma. *Cancer Lett* 286: 5-8. [Crossref]

5. Wild CP, Montesano R (2009) A model of interaction: aflatoxins and hepatitis viruses in liver cancer aetiology and prevention. *Cancer Lett* 286: 22-28. [Crossref]

6. Bagnardi V, Blangiardo M, La Vecchia C, Corrao G (2001) A meta-analysis of alcohol drinking and cancer risk. *Br J Cancer* 85: 1700-1705. [Crossref]

7. Maluccio M, Covey A (2012) Recent progress in understanding, diagnosing, and treating hepatocellular carcinoma. *CA Cancer J Clin* 62: 394-399.

8. Xia JF, Gao JJ, Inagaki Y, Kokudo N, Nakata M, et al. (2013) Flavonoids as potential anti-hepatocellular carcinoma agents: recent approaches using HepG2 cell line. *Drug Discov Ther* 7: 1-8.

9. Man YN, Liu XH, Wu XZ (2015) Chinese medicine herbal treatment based on syndrome differentiation improves the overall survival of patients with unresectable hepatocellular carcinoma. *Chin J Integr Med* 21: 49-57.

10. Chen JX, Xu QX, Wang JH, Zheng QH (2016) A case of recurrent hepatocellular carcinoma acquiring complete remission of target lesion with treatment with traditional Chinese medicine. *Integr Cancer Ther* [Epub ahead of print].

11. Yin W, Ye Q, Wang F, Liang J, Xu B, et al. (2016) ART score and hepatocellular carcinoma: an appraisal of its applicability. *Clin Res Hepatol Gastroenterol* [Epub ahead of print].

12. Xi S, Peng Y, Minuk GY, Shi M, Fu B, et al. (2016) The combination effects of Shen-Ling-Bai-Zhu on promoting apoptosis of transplanted H22 hepatocellular carcinoma in mice receiving chemotherapy. *J Ethnopharmacol* 190: 1-12.

13. Wang G, Wang RP (2013) Wang Ruiping's experience in the treatment of primary liver cancer. *Chinese J Tradit Chinese Med* 54: 152-154.

14. Xia YJ, Zhang YH (2013) The experience of syndrome differentiation of primary hepatic carcinoma. *Chinese J Tradit Chinese Med* 54: 1237–1239.

15. Liu Q, Zhang YB, Ma CH, Yue XQ, Ling CQ (2005) Analysis of literature on therapeutic methods and medicines of traditional Chinese medicine for primary liver cancer. *Zhong Xi Yi Jie He Xue Bao* 3: 260–262.

16. Liu X, Li N (2012) Regularity analysis on clinical treatment in primary liver cancer by traditional Chinese medicine. *Zhongguo Zhong Yao Za Zhi* 37: 1327-1331.

17. Sun Z, Su YH, Yue XQ (2008) Professor Ling Changquan's experience in treating primary liver cancer: an analysis of herbal medication. *Zhong Xi Yi Jie He Xue Bao* 6: 1221-1225. [Crossref]

18. Chen Z, Wang P (2012) Clinical distribution and molecular basis of traditional Chinese medicine ZHENG in cancer. *Evid Based Complement Alternat Med*: 783923.

19. Liu Z, Chen S, Cai J, Zhang E, Lan L, et al. (2013) Traditional Chinese medicine syndrome-related herbal prescriptions in treatment of malignant tumors. *J Tradit Chin Med* 33: 19-26.

20. Shi J, Wei PK (2012) Professor Wei Pin-kang's experience in treating chemotherapy induced nausea and vomiting: an analysis of herbal medication. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 32: 556-559.

21. Meng Z, Yang P, Shen Y, Bei W, Zhang Y, et al. (2009) Pilot study of huachansu in patients with hepatocellular carcinoma, nonsmall-cell lung cancer, or pancreatic cancer. *Cancer* 115: 5309-5318.

22. Qiu JX, Yang JK (1988) Experimental research and clinical observations in the treatment of advanced hepatoma by Chinese herbal drugs. *Chinese J Cancer Res* 1: 67–70.

23. Zhang Z, Liu YJ, An FL (2012) Gan Kang 6 in the treating of 82 cases of primary hepatoma. *Chinese Med* 21: 88-89.

24. Jiang L, Chen HF (2013) Weilingxian Huangqi decoction in the treating 32 cases of advanced primary hepatoma. *Shanxi Tradit Chinese Med* 34: 9-10.

25. Chen Z, Zhai XF, Su YH, Wan XY, Li J, et al. (2003) Clinical observation of cinobufacini injection used to treat moderate and advanced primary liver cancer. *Zhong Xi Yi Jie He Xue Bao* 1: 184-186.

26. Tian HQ, Li HL, Wang B, Liang GW, Huang XQ, et al. (2010) Treatment of middle/late stage primary hepatic carcinoma by Chinese medicine comprehensive therapy: a prospective randomized controlled study. *Chin J Integr Med* 16: 102-108.

27. Chen QW, Ying HF, Gao S, Shen YH, Meng ZQ, et al. (2016) Radiofrequency ablation plus chemoembolization versus radiofrequency ablation alone for hepatocellular carcinoma: a systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol* 40: 309-314.

28. Lee JK, Kim JH, Shin HK (2011) Therapeutic effects of the oriental herbal medicine Sho-saiko-to on liver cirrhosis and carcinoma. *Hepatol Res* 41: 825-837.

29. Oka H, Yamamoto S, Kuroki T, Harihara S, Marumo T, et al. (1995) Prospective study of chemoprevention of hepatocellular carcinoma with Sho-saiko-to (TJ-9). *Cancer* 76: 743-749. [Crossref]

30. Huang Z, Wang Y, Chen J, Wang R, Chen Q (2013) Effect of Xiaoaiping injection on advanced hepatocellular carcinoma in patients. *J Tradit Chin Med* 33: 34-38. [Crossref]

31. Li QS, Cao SH, Xie GM, Gan YH, Ma HJ, et al. (1994) Combined traditional Chinese medicine and Western medicine. Relieving effects of Chinese herbs, ear-acupuncture and epidural morphine on postoperative pain in liver cancer. *Chin Med J (Engl)* 107: 289-294.

32. Gao L, Wang XD, Niu YY, Duan DD, Yang X, et al. (2016) Molecular targets of Chinese herbs: a clinical study of hepatoma based on network pharmacology. *Sci Rep* 6: 24944. [Crossref]

33. Wu P, Dugoua JJ, Eyawo O, Mills EJ (2009) Traditional Chinese Medicines in the treatment of hepatocellular cancers: a systematic review and meta-analysis. *J Exp Clin Cancer Res* 28: 112. [Crossref]

34. Li WP, Hao YX, Cui HJ, Yu LL, Zhang DZ, et al. (1996) External application of Chinese medicine Qu Tong Ling in treating 144 cases of cancer pain. *Chinese J Integr Tradit West Med* 2: 23-25.

35. Yang F, Li J, Zhu J, Wang D, Chen S, et al. (2015) Hydroxysafflor yellow A inhibits angiogenesis of hepatocellular carcinoma via blocking ERK/MAPK and NF-?B signaling pathway in H22 tumor-bearing mice. *Eur J Pharmacol* 754: 105-114.

36. Zhao J, Lin W, Cao Z, Zhuang Q, Zheng L, et al. (2015) 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* 11: 357-361.

37. Lin CH, Chang CY, Lee KR, Lin HJ, Lin WC, et al. (2016) Cold-water extracts of Grifola frondosa and its purified active fraction inhibit hepatocellular carcinoma in vitro and in vivo. Exp Biol Med (Maywood) 241: 1374-1385.

38. Lin W, Zhao J, Cao Z, Zhuang Q, Zheng L, et al. (2014) Livistona chinensis seeds inhibit hepatocellular carcinoma angiogenesis in vivo via suppression of the notch pathway. *Oncol Rep* 31: 1723-1728.

39. Qian YY, Zhang H, Hou Y, Yuan L, Li GQ, et al. (2012) Celastrus orbiculatus extract inhibits tumor angiogenesis by targeting vascular endothelial growth factor signaling pathway and shows potent antitumor activity in hepatocarcinomas in vitro and in vivo. *Chin J Integr Med* 18: 752-760.

40. Cao Z, Lin W, Huang Z, Chen X, Zhao J, et al. (2013) 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* 42: 202–210.

41. Cheng J, Han W, Wang Z, Shao Y, Wang Y, et al. (2015) Hepatocellular carcinoma growth is inhibited by Euphorbia Helioscopia L. extract in nude mice xenografts. *Biomed Res Int* 2015: 601015.

42. Min L, Ling W, Hua R, Qi H, Chen S, et al. (2016) Anti-angiogenic therapy for normalization of tumor vasculature: a potential effect of Buyang Huanwu decoction on nude mice bearing human hepatocellular carcinoma xenografts with high metastatic potential. *Mol Med Rep* 13: 2518-2526.

43. Yang J, Li X, Xue Y, Wang N, Liu W (2014) Anti-hepatoma activity and mechanism of corn silk polysaccharides in H22 tumor-bearing mice. *Int J Biol Macromol* 64: 276-280. [Crossref]

44. Sun B, Meng J, Xiang T, Chen Z, Li Y, et al. (2013) Jianpijiedu fang improves survival of hepatocarcinoma mice by affecting phosphatase and tensin homolog, phosphoinositide 3-kinase, and focal adhesion kinase. *J Tradit Chin Med* 33: 479-485.

45. Tian QE, Li HD, Yan M, Cai HL, Tan QY, et al. (2012) Astragalus polysaccharides can regulate cytokine and P-glycoprotein expression in H22 tumor-bearing mice. *World J Gastroenterol* 18: 7079-7086.

46. Lin Y, Zhang Y, Shang E, Lai W, Zhu H, et al. (2016) Effect of Glycyrrhiza on the diuretic function of Euphorbia kansui: an ascites mouse model. *Evid Based Complement Alternat Med*: 7620817.

47. Fonseca AL, Cha CH (2014) Hepatocellular carcinoma: a comprehensive overview of surgical therapy. *J Surg Oncol* 110: 712-719. [Crossref]

48. Motoyama H, Kobayashi A, Yokoyama T, Shimizu A, Furusawa N, et al. (2014) Liver failure after hepatocellular carcinoma surgery. *Langenbecks Arch Surg* 399: 1047-1055.

49. Sun Z, Liang ST, Zhai XF, Lang QB, Zhou QH, et al. (2012) A traditional Chinese herbal medicine compound preparation versus interventional therapy after resection of small hepatocellular carcinoma: 22-year follow-up. *J Tradit Chin Med* 32: 156-163.

50. Zheng Z, Cho WC, Xu L, Wang J, Sze DM (2013) Lessons learnt from evidence-based approach of using Chinese herbal medicines in liver cancer. *Evid Based Complement Alternat Med*: 656351.

51. Kim KS, Jung HS, Choi WC, Eo WK, Cheon SH (2011) A case of recurred hepatocellular carcinoma refractory to doxorubicin after liver transplantation showing response to herbal medicine product, Rhus verniciflua stokes extract. *Integr Cancer Ther* 10: 299.

52. Zhong C, Li HD, Liu DY, Xu FB, Wu J, et al. (2014) Clinical study of hepatectomy combined with Jianpi Huayu therapy for hepatocellular carcinoma. *Asian Pac J Cancer Prev* 15: 5951-5957.

53. You XM, Mo XS, Ma L, Zhong JH, Qin HG, et al. (2015) Randomized Clinical Trial Comparing Efficacy of Simo Decoction and Acupuncture or Chewing Gum Alone on Postoperative Ileus in Patients With Hepatocellular Carcinoma After Hepatectomy. *Medicine (Baltimore)* 94: e1968. [Crossref]

54. Chen LW, Lin J, Chen W, Zhang W (2005) Effect of Chinese herbal medicine on patients with primary hepatic carcinoma in III stage during perioperational period: a report of 42 cases. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 25: 832–834.

55. Shu X, McCulloch M, Xiao H, Broffman M, Gao J (2005) Chinese herbal medicine and chemotherapy in the treatment of hepatocellular carcinoma: a meta-analysis of randomized controlled trials. *Integr Cancer Ther* 4: 219-229.

56. Guan CN, Cai LZ, Yue LQ, Zhang Y (2006) Clinical study on treatment of advanced primary liver cancer by Yanshu injection combining with chemotherapy. *Zhongguo Zhong Yao Za Zhi* 31: 510–512.

57. Wu D, Bao WG, Ding YH (2005) Clinical and experimental study of xiaoshui decoction in the treatment of primary liver cancer caused ascites. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 25: 1066–1069.

58. Peng W, Hu C, Shu Z, Han T, Qin L, et al. (2015) Antitumor activity of tatariside F isolated from roots of Fagopyrum tataricum (L.) gaertn against H22 hepatocellular carcinoma via up-regulation of p53. *Phytomedicine* 22: 730-736.

59. Zhang LR, Tang Y, Jiang GR (2012) The protection of yupingfeng powder on cisplatin induced oxidative damage of organs in hepatocellular carcinoma mice. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 32: 647-651.

60. Tu YS, Sun DM, Zhang JJ, Jiang ZQ, Chen YX, et al. (2014) Preparation and characterization of andrographolide niosomes and its anti-hepatocellular carcinoma activity. *J Microencapsul* 31: 307-316.

61. Hu H, Chen D, Li Y, Zhang X (2006) Effect of polypeptides in bee venom on growth inhibition and apoptosis induction of the human hepatoma cell line SMMC-7721 in vitro and Balb/c nude mice *in vivo*. *J Pharm Pharmacol* 58: 83-89.

62. Aitken KL, Hawkins MA (2014) The role of radiotherapy and chemoradiation in the management of primary liver tumours. *Clin Oncol (R Coll Radiol)* 26: 569-580. [Crossref]

63. Seong J (2009) Challenge and hope in radiotherapy of hepatocellular carcinoma. *Yonsei Med J* 50: 601-612. [Crossref]

64. Wang BF, Lin S, Bai MH, Song LQ, Min WL, et al. (2014) Effects of SSd combined with radiation on inhibiting SMMC-7721 hepatoma cell growth. *Med Sci Monit* 20: 1340-1344. [Crossref]

65. Zeng ZC, Tang ZY, Yang BH, Liu KD, Wu ZQ, et al. (2002) Comparison between radioimmunotherapy and external beam radiation therapy for patients with hepatocellular carcinoma. *Eur J Nucl Med Mol Imaging* 29: 1657-1668.

66. Kim BS, Chung HC, Seong JS, Suh CO, Kim GE (1992) Phase II trial for combined external radiotherapy and hyperthermia for unresectable hepatoma. *Cancer Chemother Pharmacol* (31 Suppl): S119–127.

67. Han JQ, Chen SD, Zhai LM (1997) Clinical study of combined Chinese herbal medicine with move stripe field radiation in treating primary hepatocellular carcinoma. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 17: 465–466.

68. Yu EX (1992) Combined moving strip whole liver irradiation and traditional Chinese medicine for large liver cancer. *Zhonghua Zhong Liu Za Zhi* 14: 57-60.

69. Mahnken AH, Bruners P, Günther RW (2008) Techniques of interventional tumor therapy. *Dtsch Arztebl Int* 105: 646-653. [Crossref]

70. Li DJ, Xu XH, Bao D, Xue F, Dai DL (2009) Effects of kanglaite capsules combined with transcatheter arterial chemoembolization (TACE) on patients with mid or late-stage primary hepatocellular carcinoma (HCC). *Chinese-German J Clin Oncol* 8: 65-68.

71. Xu L, Wang S, Zhuang L, Lin J, Chen H, et al. (2016) 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* 15: 349–357.

72. Tang CW, Zhu M, Feng WM, Bao Y, Zheng YY (2016) Chinese herbal medicine, Jianpi Ligan decoction, improves prognosis of unresectable hepatocellular carcinoma after transarterial chemoembolization: a retrospective study. *Drug Des Devel Ther* 10: 2461-2466.

73. Chen XX, Zhang B, Zhang YQ, Hung GX, Chen MS, et al. (2002) Treatment of hepatic functional reserve injury after TACE in hepatocellular carcinoma with Chinese herbal medicines. *Ai Zheng* 21: 547-549.

74. Hou EC, Lu YX (2009) Primary hepatocarcinoma treated by traditional Chinese medicine combined with transcatheter arterial chemoembolization. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 29: 225-227.

75. Dong J, Zhai X, Chen Z, Liu Q, Ye H, et al. (2016) Treatment of huge hepatocellular carcinoma using cinobufacini injection in transarterial chemoembolization: a retrospective study. *Evid Based Complement Alternat Med*: 2754542.

76. Weng LL, Xiang JF, Lin JB, Yi SH, Yang LT, et al. (2014) Asparagus polysaccharide and gum with hepatic artery embolization induces tumor growth and inhibits angiogenesis in an orthotopic hepatocellular carcinoma model. *Asian Pac J Cancer Prev* 15: 10949-10955.

77. Shao ZX, Cheng ZG, Yin X (2001) Clinical study on treatment of middle-advanced stage liver cancer by combined treatment of hepatic artery chemoembolization with gan'ai no. I and no. II. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 21: 168-170.

78. Zhang W, Ma YZ, Song L, Wang CH, Qi TG, et al. (2014) Effect of cantharidins in chemotherapy for hepatoma: a retrospective cohort study. *Am J Chin Med* 42: 561-567. [Crossref]

79. Wu GL, Zhang L, Li TY, Chen J, Yu GY, et al. (2010) Short-term effect of combined therapy with Jinlong capsule and transcatheter arterial chemoembolization on patients with primary hepatic carcinoma and its influence on serum osteopontin expression. *Chin J Integr Med* 16: 109-113.

80. Meng MB, Wen QL, Cui YL, She B, Zhang RM (2011) Meta-analysis: traditional Chinese medicine for improving immune response in patients with unresectable hepatocellular carcinoma after transcatheter arterial chemoembolization. *Explore (NY)* 7: 37-43.

81. Chen ZX1, Zhang SJ, Hu HT, Sun BG, Yin LR (2007) Clinical study of method of strengthening body resistance and disintoxication disintoxication in patients with HCC of post-TACE. *Zhongguo Zhong Yao Za Zhi* 32: 1211-1213. [Crossref]

82. Yu Y, Lang Q, Chen Z, Li B, Yu C, et al. (2009) The efficacy for unresectable hepatocellular carcinoma may be improved by transcatheter arterial chemoembolization in combination with a traditional Chinese herbal medicine formula: a retrospective study. *Cancer* 115: 5132-5138.

83. Meng MB, Cui YL, Guan YS, Ying Z, Zheng MH, et al. (2008) Traditional Chinese medicine plus transcatheter arterial chemoembolization for unresectable hepatocellular carcinoma. *J Altern Complement Med* 14: 1027-1042.

84. Lin LZ, Zhou DH, Liu K, Wang FJ, Lan SQ, et al. (2005) Analysis on the prognostic factors in patients with large hepatocarcinoma treated by shentao ruangan pill and hydroxycamptothecine. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 25: 8-11.

85. Chen Z, Chen HY, Lang QB, Li B, Zhai XF, et al. (2012) Preventive effects of jiedu granules combined with cinobufacini injection versus transcatheter arterial chemoembolization in post-surgical patients with hepatocellular carcinoma: a case-control trial. *Chin J Integr Med* 18: 339-344.

86. Zhai XF, Chen Z, Li B, Shen F, Fan J, et al. (2013) Traditional herbal medicine in preventing recurrence after resection of small hepatocellular carcinoma: a multicenter randomized controlled trial. *J Integr Med* 11: 90–100.

87. Cheng JH, Chang G, Wu WY (2001) A controlled clinical study between hepatic arterial infusion with embolized curcuma aromatic oil and chemical drugs in treating primary liver cancer. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 21: 165-167.

88. Feng YL, Ling CQ, Li B (2005) Clinical study on integrative medicine for preventing and treating post-transcatheter arterial chemoembolization. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 25: 534-536.

89. Kim YS, Lim HK, Rhim H, Lee MW (2014) Ablation of hepatocellular carcinoma. *Best Pract Res Clin Gastroenterol* 28: 897-908. [Crossref]

90. Lou HZ, Pan HM, Jin W (2007) Clinical study on treatment of primary liver cancer by Aidi injection combined with cool-tip radiofrequency ablation. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 27: 393-395.

91. Lin JJ, Jin CN, Zheng ML, Ouyang XN, Zeng JX, et al. (2005) Clinical study on treatment of primary hepatocellular carcinoma by Shenqi mixture combined with microwave coagulation. *Chin J Integr Med* 11: 104-110.

92. Zhao HJ, Du J, Chen X (2012) Clinical study of Fuzheng Yiliu recipe combined with microwave ablation on hepatocellular carcinoma. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 32: 32-34.

93. Liang P, Wang Y (2007) Microwave ablation of hepatocellular carcinoma. *Oncology* 72(Suppl 1): 124-131. [Crossref]

94. Bai GD, Lian ZP, Huang DP, Guan Y (2009) The effect of argon helium knife treatment on the immune function of patients with advanced hepatocellular carcinoma. *Liaoning J Tradit Chinese Med*: 1535–1537.

95. Ting SC, Qian Y, Wu XX (2012) PEIT plus Qinggan anticancer prescription in the treatment of primary hepatocellular carcinoma in 52 cases. *J Tradit Chinese Med* 53: 1144-1145.

96. Xu K, Luo HY, Li LN (2005) Clinical study on comprehensive treatment of primary liver cancer mainly with Chinese medicinal perfusion/embolization. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 25: 299-302.

97. Wang B, Tian HQ, Liang GW (2009) Effect of Ganji recipe combined with Fructus Bruceae oil emulsion intervention on quality of life in patients with advanced primary hepatic cancer. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 29: 257-260.

98. Chen QW, Ying HF, Gao S, Shen YH, Meng ZQ, et al. (2016) Radiofrequency ablation plus chemoembolization versus radiofrequency ablation alone for hepatocellular carcinoma: a systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol* 40: 309–314.

99. Liu YM, Qin H, Wang CB, Fang XH, Ma QY (2007) Comparison of different interventional therapies for primary liver cancer. *Zhonghua Zhong Liu Za Zhi* 29: 232-235.

100. Zhang B, Huang G, Zhang Y, Chen X, Hu P, et al. (2004) Clinical observation on prevention of "jia wei si jun zi tang" from damage of hepatic reserving function after intervention of liver cancer. Zhong Yao Cai 27: 387-389.

101. Chiu J, Yau T, Epstein RJ (2009) Complications of traditional Chinese/herbal medicines (TCM)-a guide for perplexed oncologists and other cancer caregivers. *Support Care Cancer* 17: 231-240.

102. Lencioni R, Llovet JM (2010) Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. *Semin Liver Dis* 30: 52-60. [Crossref]

103. Li DT, Ling CQ, Lang QB, Zhu DZ, Yu CQ, et al. (2007) Construction of a therapeutic effect evaluation system for patients with primary liver cancer based on syndrome differentiation in traditional Chinese medicine. *Zhong Xi Yi Jie He Xue Bao* 5: 15-22.

104. Tate Thigpen J (2015) Contemporary phase III clinical trial endpoints in advanced ovarian cancer: assessing the pros and cons of objective response rate, progression-free survival, and overall survival. *Gynecol Oncol* 136: 121-129.

105. Wang Z, Jiang C, Chen W, Zhang G, Luo D, et al. (2014) Baicalein induces apoptosis and autophagy via endoplasmic reticulum stress in hepatocellular carcinoma cells. *Biomed Res Int*: 732516.

106. Qu L, Zhang H, Yang Y, Yang G, Xin H, et al. (2016) Corosolic acid analogue, a natural triterpenoid saponin, induces apoptosis on human hepatocarcinoma cells through mitochondrial pathway *in vitro*. *Pharm Biol* 54: 1445-1457.

107. Zhang K, Rui X, Yan X (2014) Curcumin inhibits the proliferation and invasiveness of MHCC97-H cells via p38 signaling pathway. *Drug Dev Res* 75: 463-468.

108. Shen X, Zhang Y, Feng Y, Zhang L, Li J, et al. (2014) Epigallocatechin-3 gallate inhibits cell growth, induces apoptosis and causes S phase arrest in hepatocellular carcinoma by suppressing the AKT pathway. *Int J Oncol* 44: 791-796.

109. Zhao JL, Zhao J, Jiao HJ (2014) Synergistic growth suppressive effects of quercetin and cisplatin on HepG2 human hepatocellular carcinoma cells. *Appl Biochem Biotechnol* 172: 784-791.

110. Ma H, Fan Q, Yu J, Xin J, Zhang C (2013) Novel microemulsion of tanshinone IIA, isolated from Salvia miltiorrhiza Bunge, exerts anticancer activity through inducing apoptosis in hepatoma cells. *Am J Chin Med* 41: 197-210.

111. Tian QE, De Li H, Yan M, Cai HL, Tan QY, et al. (2012) Effects of Astragalus polysaccharides on P-glycoprotein efflux pump function and protein expression in H22 hepatoma cells in vitro. *BMC Complement Altern Med* 12: 94.

112. Wang YX, Gu XX, Geng D, Sun HY, Wang CM, et al. (2014) Differentiation of bel-7402 human hepatocarcinoma cells induced by aqueous extracts of fresh gecko (AG) and its anti-tumor activity *in vivo*. *J Ethnopharmacol* 155: 1583-1588.

113. Zhang Q, Liu J, Liu B, Xia J, Chen N, et al. (2014) Dihydromyricetin promotes hepatocellular carcinoma regression via a p53 activation-dependent mechanism. *Sci Rep* 4: 4628.

114. Liu Q, Chen W, Jiao Y, Hou J, Wu Q, et al. (2014) Pulsatilla saponin A, an active molecule from Pulsatilla chinensis, induces cancer cell death and inhibits tumor growth in mouse xenograft models. *J Surg Res* 188: 387-395.

115. Ding W, Zhang L, Kim S, Tian W, Tong Y, et al. (2015) Arsenic sulfide as a potential antiâ€'cancer drug. *Mol Med Rep* 11: 968-974. [Crossref]

116. Perng DS, Tsai YH, Cherng J, Kuo CW, Shiao CC, et al. (2016) Discovery of a novel anti-cancer agent targeting both topoisomerase I and II in hepatocellular carcinoma Hep 3B cells in vitro and in vivo: Cinnamomum verum component 2-methoxycinnamaldehyde. *J Drug Target* 24: 624-634.

117. Hu Y, Wang S, Wu X, Zhang J, Chen R, et al. (2013) Chinese herbal medicine-derived compounds for cancer therapy: a focus on hepatocellular carcinoma. *J Ethnopharmacol* 149: 601-612. [Crossref]

118. Hsu YL, Kuo PL, Tzeng TF, Sung SC, Yen MH, et al. (2008) Huang-lian-jie-du-tang, a traditional Chinese medicine prescription, induces cell-cycle arrest and apoptosis in human liver cancer cells *in vitro* and *in vivo*. *J Gastroenterol Hepatol* 23(7 Pt 2): e290-299.

119. Hu B, An HM, Shen KP, Xu L, Du Q, et al. (2011) Modified Yi Guan Jian, a Chinese herbal formula, induces anoikis in Bel-7402 human hepatocarcinoma cells in vitro. *Oncol Rep* 26: 1465-1470.

120. Liu XQ, Hu XJ, Xu HX, Zeng XY (2013) Xiaochaihu decoction attenuates the vicious circle between the oxidative stress and the ALP inactivation through LPS–catecholamines interactions in gut, liver and brain during CCI4+ ethanol-induced mouse HCC. *BMC Complement Altern Med* 13: 375.

121. Jia QA, Wang ZM, Ren ZG, Bu Y, Xie XY, et al. (2013) Herbal compound "Songyou Yin" attenuates hepatoma cell invasiveness and metastasis through downregulation of cytokines secreted by activated hepatic stellate cells. *BMC Complement Altern Med* 13: 89.

122. Fang Y, Yang Z, Ouyang H, Wang R, Li J, et al. (2016) Synthesis and biological evaluation of Hederacolchiside A1 derivatives as anticancer agents. *Bioorg Med Chem Lett* 26: 4576-4579. [Crossref]

123. Xu G, Yu X, Zhang J, Sheng Y, Liu G, et al. (2016) Robust aptamer-polydopamine-functionalized M-PLGA-TPGS nanoparticles for targeted delivery of docetaxel and enhanced cervical cancer therapy. *Int J Nanomedicine* 11: 2953-2965.

124. Pan P, Wu Y, Guo ZY, Wang R, Wang YJ, et al. (2012) Antitumor activity and immunomodulatory effects of the intraperitoneal administration of Kanglaite in vivo in Lewis lung carcinoma. *J Ethnopharmacol* 143: 680-685.

125. Guo J, Pan W, Qian D, Duan JA, Shang E, et al. (2013) Analgesic activity of DaChuanXiongFang after intranasal administration and its potential active components in vivo. *J Ethnopharmacol* 150(2): 649-654.

126. Kesarwani K, Gupta R, Mukerjee A (2013) Bioavailability enhancers of herbal origin: an overview. *Asian Pac J Trop Biomed* 3: 253-266. [Crossref]

127. Woo JS, Kim TS, Park JH, Chi SC (2007) Formulation and biopharmaceutical evaluation of silymarin using SMEDDS. *Arch Pharm Res* 30: 82-89. [Crossref]

128. Li YL, Li J, Yan CY, Lai ZF, Hu GJ (2014) Chinese medicine single-walled carbon nanotube targeting compound for antitumor therapy: a feasible way? *Chin J Integr Med* 20: 63-67.

129. Passerini N, Perissutti B, Albertini B, Franceschinis E, Lenaz D, et al. (2012) A new approach to enhance oral bioavailability of Silybum Marianum dry extract: association of mechanochemical activation and spray congealing. *Phytomedicine* 19: 160-168.

130. Ghosh D, Choudhury ST, Ghosh S, Mandal AK, Sarkar S, et al. (2012) Nanocapsulated curcumin: oral chemopreventive formulation against diethylnitrosamine induced hepatocellular carcinoma in rat. *Chem Biol Interact* 195: 206-214.

131. Feng N, Wu P, Li Q, Mei Y, Shi S, et al. (2008) Oridonin-loaded poly (epsilon-caprolactone)-poly (ethylene oxide)-poly (epsilon-caprolactone) copolymer nanoparticles: preparation, characterization, and antitumor activity on mice with transplanted hepatoma. *J Drug Target* 16: 479-485.