

Traditional Chinese Medicine Combined With Other Therapies for Treatment of Hepatocellular Carcinoma in Clinical Trials

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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.

Keywords: Traditional Chinese medicine; Hepatocellular carcinoma; Recent progress; Clinical trial; Current problems

1. 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.

2. 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 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.

3. 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] (as shown in 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].

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	[9]
Gan kang 6	9.76% tumor effective rate, 26.83% symptoms effective rate	18.29% tumor effective rate, 81.71% symptoms effective rate	[23]
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	[25]
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	[26]
Xiaoaipng 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	[30]
Different TCM	6 months MST, 0% 5-year OS rate	13 months MST, 2.61% 5-year OS rate	[32]
Qu tong ling	4.81±2.21h PRST	6.42±1.24h PRST	[34]

4. 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 (as shown in Table 2). In the following section, the combination of TCM with various other therapies will each be described.

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	[49]
	Ruanjianhugan tablets and resection	43.87 months median OS, 5-, 10-, and 15-year OS was 33.34%, 55.58% and 9.26% respectively		
	Jianpi Huayu	22.6 months median DFS, 49.8 months median survival, 1-, 3- and 5-year DFS and OS are different	28.7 months median DFS, 52.6 months median survival, 1-, 3- and 5-year DFS and OS are different	[52]

	Simo decoction	16.5d hospital stay, 29.6h first peristalsis	14.0d hospital stay, 19.6h first peristalsis	[53]
	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	[54]
Chemotherapy	Shen-Ling-Bai-Zhu	Tumor sizes were decreased - 52%	Tumor sizes were decreased - 58%	[12]
	Chinese herbal medicine	No these functions	Improved survival, tumor response increased	[55]
TACE	Jian Pi Li Qi	12 PES increased significantly after TACE	7 PES relieved significantly, liver function improved	[71]
	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	[72]
	Cinobufacini injection	23.1% objective response rate	53.6% objective response rate, less adverse events	[75]
	Asparagus polysaccharide or gum	No these functions	Liver tumor growth and angiogenesis were significantly inhibited, immunomodulatory functions were improved	[76]
	Cantharidins	Lower overall efficient rate and KPS	Higher overall efficient rate and KPS, lower WBC count, relieving side effects and improving the QOL	[78]
	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	[79]
	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	[82]
	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	[84]
	Jiedu granules, Cinobufacini injection (TACE+Resection)	8.03 months PFS, 39.90 months MST, 1-, 2-, 3-, 4- and 5-year PFS rate and SR were different respectively	18.07 months PFS, 49.53 months MST, 1-, 2-, 3-, 4- and 5-year PFS rate and SR were different respectively	[85]
	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	[85]

Microwave coagulation	Shenqi mixture	55.56% effective rate, 12-month, 18-month, 24-month SR and the reoccurrence rate were different respectively	75.00% effective rate, 12-month, 18-month, 24-month SR and the reoccurrence rate were different respectively	[91]
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	[92]
Invention therapy	Ganji decoction, Ailitong etc.	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	[28]
Invention therapy	Ganji recipe, <i>Fructus Bruceae</i> 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	[97]

4.1 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.

4.2 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) has been adopted in the clinical treatment of HCC. IC allows 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 noisome [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.

4.3 Combination of TCM and radiotherapy for treatment of HCC

Keratomy 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 trans arterial 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 radio sensitivity 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.

4.4 Combination of TCM and interventional therapy for treatment of HCC

4.4.1 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 Trans Cather 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 post embolization 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.

4.4.2 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] has 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 + keratectomy [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.

5. 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.

5.1 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.

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

The anticancer mechanism of some herbal formulas and extracts has 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 has 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.

5.3. 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.

5.4 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.

6. CONCLUSION

In summary, regardless of used alone or in combination with other therapies, TCM have 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.

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 15Minutes; 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, transcatheter arterial chemoembolization; TBIL, total bilirubin; TCM, traditional Chinese medicine; WBC, white blood cell; WM, western medicine.

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