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.

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 chemotherapy; 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; PR: 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

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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 progression 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 great 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-scale, 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 |
|-------------------|---------|------------|
| Different Chinese medicines | 12 months MST, 43.4% 1-year SR, 26.6% 2-year SR | Man et al. (2015) |
| Different Chinese medicines | Control group | TCM treatment group |
| Different Chinese medicines | 36 months MST, 76.7% 1-year SR, 51.6% 2-year SR | |
| TCM prescription | 13.4% 1-year SR | | Qiu et al. (1988) |
| Gan kang 6 | 9.76% tumor effective rate, 26.83% 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 | | Chen et al. (2003) |
| Sho-saiko-to | 34% cumulative incidence, 60% survival curve | | Oka et al. (1995) |
| Xiaoaiping injection | 24.5 weeks MST, 15 weeks PFS, 25.0% cumulative SR of 6-months | | Huang et al. (2013) |
| Different TCM | 6 months MST, 0% 5-year OS rate | | Gao et al. (2016) |
| Qu tong ling | 4.8±2.2±2.1h PRST | | Li et al. (1996) |
| Jia Wei Si Jun Zi Tang | ICGR15 15.36%-9.82% before second treatment, 19.12%-9.96% 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 |
|----------------------|-------------------|---------|------------|
| Hepatectomy | Ruanjianhugan tablets | 20.77 months median OS, 5-, 10-year OS rate was 13.84% and 13.84% 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 | Xiu et al. (2001) |
| Chinese herbal medicine | All these indexes lower than Chinese herbal medicine group | | |
| Jia Pi 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%, 74.0% and 37.4% respectively | Zhong et al. (2014) |
| Simo decoction | 16.5d hospital stay, 29.6h first peristalsis | You et al. (2015) |
| Jiedu xiaosheng yin, Fuzheng yiliu recipe | 30.0% accumulative 3-year SR, 80.0% 2-year recurrence rate | Chen et al. (2005) |
| Chemotherapy | Shen-Ling-Bai-Zhu | Tumor sizes were decreased -52% | 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 | Han et al. (1997) |
| Jian Pi Li Qi group | 1-, 3- and 5-year SR was 85.77%-36.34%, 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) |
has been adopted in the clinical treatment of HCC. IC allow drugs to reach carcinoma nests with increased dosage directly and achieved a better result [57]. Combination therapy of the IC and other therapies, such as microwave coagulation, transarterial chemoembolization (TACE), radiofrequency ablation, hepatic arterial infusion, and so on, has been adopted in the clinical treatment of HCC. IC allow drugs to reach carcinoma nests with increased dosage directly and achieved a better result [57]. Combination therapy of the IC and other therapies, such as microwave coagulation, transarterial chemoembolization (TACE), radiofrequency ablation, hepatic arterial infusion, and so on, has been adopted in the clinical treatment of HCC. IC allow drugs to reach carcinoma nests with increased dosage directly and achieved a better result [57]. Combination therapy of the IC and other therapies, such as microwave coagulation, transarterial chemoembolization (TACE), radiofrequency ablation, hepatic arterial infusion, and so on, has been adopted in the clinical treatment of HCC. IC allow drugs to reach carcinoma nests with increased dosage directly and achieved a better result [57]. Combination therapy of the IC and other therapies, such as microwave coagulation, transarterial chemoembolization (TACE), radiofrequency ablation, hepatic arterial infusion, and so on, has been adopted in the clinical treatment of HCC. IC allow drugs to reach carcinoma nests with increased dosage directly and achieved a better result [57].

### 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 unsatisfactory curative effects [64]. Radiotherapy also often causes unsatisfactory curative effects [64]. Radiotherapy also often causes unsatisfactory curative effects [64]. Radiotherapy also often causes unsatisfactory curative effects [64].

### Table: Treatment outcomes for hepatocellular carcinoma

| Treatment Method | OS Probability | 3-Year SR | Quality of Life Improvement | Bone Marrow Inhibition | Tumor Persistence | Side Effects | Overall Reaction Rate | 2-Year SR | 5-Year SR |
|------------------|----------------|----------|----------------------------|------------------------|------------------|-------------|-----------------------|----------|----------|
| TACE+Resection   | 96.2%          | 77.7%    | 83.3%                      | 80.8%                  | 22.2%            | 26.2%       | 75.0%                 | 17.3%    | 19.7%    |
| TACE+Resection   | 96.2%          | 77.7%    | 83.3%                      | 80.8%                  | 22.2%            | 26.2%       | 75.0%                 | 17.3%    | 19.7%    |
| TACE+Resection   | 96.2%          | 77.7%    | 83.3%                      | 80.8%                  | 22.2%            | 26.2%       | 75.0%                 | 17.3%    | 19.7%    |
| TACE+Resection   | 96.2%          | 77.7%    | 83.3%                      | 80.8%                  | 22.2%            | 26.2%       | 75.0%                 | 17.3%    | 19.7%    |
| TACE+Resection   | 96.2%          | 77.7%    | 83.3%                      | 80.8%                  | 22.2%            | 26.2%       | 75.0%                 | 17.3%    | 19.7%    |

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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 transcatheter 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 unresectable 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

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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 hydrophilic drugs and then improve the therapeutic effect of TCM. Therefore, strengthening the clinical application and isolation of TCM will be of great value for the development of future TCM application.

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.

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