Chapter 2

Liver Cancer Treatment by Chinese Medicines and their Active Compounds

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Abstract

Recent studies have indicated that traditional Chinese medicines (CMs) and their active compounds play an important role in liver cancer treatment by preventing tumor formation, inhibiting tumor growth, metastasis and recurrence as well as improving the quality of life and reducing side effects of radiotherapy and chemotherapy. Mechanism studies have proved the advantage of multicomponent, multitarget and multipathway combinational regulation by CMs in liver cancer treatment. This chapter emphatically introduces the molecular mechanisms underlying liver cancer treatment by CMs. In addition, we also put forward discussion on existing obstacles and prospect of the future development on liver cancer treatment using CMs, in terms of providing a comprehensive understanding of action of CMs in liver cancer treatment.

Keywords: TCM, Chinese medicines, Chinese herbal medicines, Anticancer, Antimetastasis, Antiangiogenesis, adjuvant therapy, complementary, alternative treatment

1. Introduction

Primary liver cancer is a serious disease threatening human health. It was the sixth most frequent cancer, and the second leading cause of cancer death worldwide according to the reports from the International Liver Cancer Association in 2014 [1]. The most common type of liver cancer is hepatocellular carcinoma (HCC), which is originated from hepatocyte. Other types of liver cancer, such as hepatoblastoma and intrahepatic cholangiocarcinoma, are relatively uncommon. Recognized risk factors for liver cancer include viral hepatitis B or C infection, obesity and alcohol abuse. In developing countries such as African countries and China, Hepatitis B or C is the major cause of liver cancer, whereas in developed countries such

as the European Union and United States, the predominant cause of liver cancer is cirrhosis caused by alcohol abuse or obesity [2]. In addition, inherited factor may also increase the risk of liver cancer. Recent studies have found that some patients developed liver cancer with inherited susceptible genes from their parents [3]. Usually, liver cancer has no symptoms at the early stages; with the tumor progression, symptoms such as yellow skin, abdominal pain, abdominal mass, nausea or liver dysfunction appear and rapidly deteriorate. Generally, the prognosis of liver cancer is poor, because only 10–20% patients with early detection can receive curative resection surgery. In addition, surgical resection is unavailable for cirrhotic patients as increased risk of fatal complications may occur during resection on cirrhotic livers [4]. Other conventional cancer treatment options such as radiation and chemotherapy are not routinely used for liver cancer as the liver is chemotherapy-refractory and not tolerant to radiation [5, 6]. In recent decades, several novel targeted therapies have been developed for liver cancer treatment. The National Comprehensive Cancer Network (NCCN) guidelines recommend sorafenib as the standard frontline therapy for patients with unresectable HCC but with well-preserved liver function [7, 8]. Other locoregional or adjuvant therapies such as the percutaneous ablation (ethanol injection and radiofrequency ablation), intra-arterial radiolabeled lipiodol, intra-arterial chemotherapy, transarterial chemoembolization (TACE), interferon, adoptive immunotherapy and complementary and alternative medicine are recommended for providing opportunity for liver transplantation or extending disease-free survival and improving survival quality. For patients who are diagnosed with early stage liver cancer, the 5-year survival rate is about 31%. If the tumor has invaded to the surrounding organs or lymph nodes, the 5-year survival rate will decrease to 11%. If the cancer has metastasized to distant organs, the 5-year survival rate is only 3% [9].

Traditional Chinese medicine (TCM) is one of the most popular complementary and alternative medicine in cancer patients worldwide. In China, TCM is based on the foundation of about 2500 years of folk medical practice, which have been covered by the National Health Insurance Program and supported by the government in both Mainland of China and Taiwan. Different from the western medicines that are based on modern human anatomy and pathology, TCM is mainly focused on the identification of functional entities. In the view of TCM, health is based on the harmonious interaction of the internal functional entities and the external environment. The primary functional entities used by TCM include gas (Qi), blood (Xie), internal organs (Zang-fu) and the meridians (Jing-luo) that are main channels of communication of Qi and Xie in the body and link Zang-Fu with the superficial areas of the body [10, 11]. There are various forms of TCM, which have been used for cancer patients, such as the herbal remedies, acupuncture, moxibustion, breathing exercise and dietary therapy. These therapies may have potential in improving the overall survival in cancer patients and the survival quality.

2. The understanding of liver cancer in traditional Chinese medicine

In TCM, liver cancer is associated with the presence of an "abdominal mass" called "zheng jia" (癥瘕). "Zheng" (癥) means fixed mass in the abdomen with fixed pain, while "Jia" (瘕)

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refers to abdominal mass occurs intermittently with no fixed pain. According to TCM literature, the symptoms of liver cancer include abdominal distention, jaundice, abdominal fullness and oppression. Those symptoms can be concluded as "Jiju" (积聚), which means syndromes caused by abdominal lump with pain or swelling. In TCM, the causes of liver cancer can be divided into internal factors and external factors. The internal factors include individual congenital constitution and emotional conditions. The emotions are considered as the major internal causes of liver cancer in TCM. Emotions are regarded as internal, normal, physiological response to stimulus from the external factors. The negative emotions with high intensity and prolonged duration may cause serious damage to the internal organs and influence the healthy condition of the whole body. External factors include unhealthy dietary habits and lifestyle such as alcohol beverage and contaminated food or over exhaustion. These factors can lead to spleen and body disharmony. Other external factors such as the environment also play an important role in the process of tumorigenesis. For example, the wet climate is considered as an induction factor for liver cancer in TCM. Both internal and external factors may cause stagnation of qi, spleen deficiency and the accumulation of dampness, which can eventually lead to liver cancer.

3. The role of Chinese medicines and their active compounds in liver cancer treatment

3.1. Chinese medicines and their active compounds for preventing liver cancer

From a TCM point of view, a good doctor should prevent and cure potential disease in the initiating stage. "Treating before getting illness" is one of the preponderant thoughts of TCM in dealing with disease and health. It is important to prevent the occurrence of liver cancer by keeping healthy diet and lifestyle according to the TCM theories. As we have discussed earlier, spleen deficiency may cause the occurrence of liver cancer. Symptoms such as ascites and abdominal distention are all related to spleen deficiency. According to the relationship among the TCM five internal organs (heart, liver, spleen, lungs and kidneys), the spleen and the liver can influence on each other. Therefore, spleen deficiency can also restrict the liver function. In order to strengthen spleen health and protect liver function, people should avoid taking too much spicy and "cold" food such as pepper, green beans and cold water. Alcohol beverage can also induce spleen deficiency by aggravating the dampness in the body. But moderate drinking are beneficial for preventing liver diseases such as liver cancer according to TCM theories [12].

Many Chinese medicines (CMs) and its active compounds are effective in reducing inflammation as confirmed by modern science [13, 14]. Recent studies have demonstrated that inflammation is a major stimulus for hepatic carcinogenesis and some CMs may prevent liver cancer by inhibiting inflammation in liver. Xiao Chai Hu Tang (XCHT) is an herbal medicine formula used in some Asian countries for treating chronic viral liver diseases. According to the TCM theories, XCHT can modulate Qi activity and balance between Yin and Yang. Recent studies found that XCHT can prevent chronic hepatitis C-related liver cancer by suppressing

inflammation and inhibiting fibrosis in the liver [15]. Shi Quan Da Bu Tang (SQDBT) is a classic TCM herbal diet formula that was documented in the "Tai Ping Imperial Grace Formulary" in Song dynasty. In TCM, SQDBT were used to regulate Qi and treat Yang deficiency. Modern scientific research show that SQDBT can relieve chronic viral liver diseases by reducing inflammatory processes and controlling serum alanine transaminase (ALT) levels, thus it may prevent liver cancer development [16]. Other TCM herbal extracts or isolates such as the Salvia Miltiorrhiza extracts, Schisandra chinensis extracts, silymarin, glycyrrhizin, baicalein and baicalin may prevent liver cancer by relieving chronic liver diseases associated hepatic steatosis and fibrosis [17–21].

3.2. Chinese medicines and their active compounds for inhibiting liver cancer development

Invigorating Qi and strengthening the spleen; relieving Qi stagnancy in liver, clearing heat and detoxifying, activating blood circulation to dissipate blood stasis, supplementing Qi and nourishing yin are the main principles in treating primary liver cancer with TCM. Inhibiting tumor growth, suppressing metastasis and preventing recurrence with TCM is the key to restrain liver cancer development. According to a large-scale cohort study in Taiwan, Jia Wei Xiao Yao San (JWXYS) and Chai Hu Shu Gan Tang (CHSGT) are the most common TCM prescriptions for liver cancer treatment. These TCM formulae can significantly inhibit tumor development and improve survival in patients with primary liver cancer [22]. JWXYS are used for invigorating the spleen and nourishing blood, it is effective for relieving Qi stagnancy in liver. Besides its antihepatoma effects, JWXYS can also inhibit colon cancer and breast cancer [23, 24]. CHSGT are also used for dispersing the Qi stagnancy in liver. Different from the JWXYS that focuses on invigorating the spleen, CHSGT is mainly applied for activating Qi movement and relieving pain. Both of these formulae have been safely used in liver cancer treatment for patients in China, Taiwan and Hong Kong, with few side effects being reported. Some pharmacological studies also revealed that a lot of CMs extracts or isolates could inhibit liver cancer growth or metastasis both *in vitro* and *in vivo*. This includes but not limited to Coptidis Rhizome extracts, Radix Bupleuri extracts, Radix Salvia Miltiorrhiza extracts, silymarin, berberine, Wogonin, bufalin and curcumin [25–28].

3.3. Chinese medicines and their active compounds for improving the quality of life and reducing the side effects of conventional therapy in liver cancer patients

As most of the liver cancer patients are diagnosed with late-stage cancer, only 20% patients may have the chance to receive curative treatment. In this case, improving the quality of life and reducing the side effects of conventional therapy are very important for liver cancer patients. The common side-effects of conventional therapies, such as nausea, vomiting, fever, abdominal pain, loss of appetite, alopecia and myelosuppression may lead to noncompliance of treatment and thus affect treatment outcomes and reduce the quality of life. According to a series of randomized clinical trials, CMs are effective in extending survival time, improving quality of life, and reducing side effects of conventional therapies for liver cancer patients [29]. For example, Ophiopogonis Radix and Galli Gigerii Endothelium Corneum (Ji Nei Jing) are most commonly used CMs for appetite improvement; Astragali Radix is widely used for

alleviating fatigue; Artemisiae Scopariae Herba is recommended for abating jaundice; Toosendan Fructus and Corydalis Rhizoma are effective in relieving abdominal pain; Pericarpium Arecae, Polyporus, Poria can be used to treat ascites [26].

4. The molecular mechanism on liver cancer treatment by Chinese medicines and their active compounds

4.1. Traditional Chinese medicines and its active compounds for inhibiting the proliferation and inducing cell death in liver cancer cells

Jie Du Xiao Zheng Yin (JDXZY) is a typical TCM formula for liver cancer treatment. Recent studies have found that JDXZY can suppress the proliferation of liver cancer cells in a dose- and time-dependent manner [30]. *In vivo* studies also confirmed that JDXZY could increase the tumor apoptotic index and reduce tumor size in nude mice. Mechanism studies showed that JDXZY may induce human hepatoma HepG2 cell apoptosis by mitochondrial-related pathway. Treatment with JDXZY can activate caspase-9 and caspase-3 as well as up-regulate the ratio of Bax/Bcl-2, which may partially demonstrate its antihepatoma effects. In addition, another study also found that JDXZY could inhibit the proliferation of HepG2 cells by arresting the cell cycle at the G0/G1 phase [31].

Bufalin is a digoxin-like agent isolated from Chansu which is a precious CMs extracted from parotoid glands of toads. Previous studies found that bufalin exhibited significant anticancer activities in many cancer cell lines *in vitro* and *in vivo*. A recent research showed that bufalin can suppress AKT-related signaling pathway in HepG2 and HCCLM3 cell lines. After bufalin treatment, the proliferation-related proteins in AKT/GSK3beta/beta-catenin/E-cadherin-signaling pathway were significantly inhibited [32]. Thus, bufalin may be a potential antihepatoma agent by inhibiting the proliferation of cancer cell.

Gekko swinhonis Guenther also called ShouGong in TCM; it was a widely used anticancer drug in China for hundreds of years. Modern science has demonstrated that one of the major active components in *Gekko swinhonis* Guenther is sulfated polysaccharide–protein complex (GSPP). Previous studies showed that GSPP can suppress the proliferation of liver cancer cells and arrest the cell cycle in SMMC-7721 cells with little direct toxicity [33]. In addition, Gepsin, the monomeric protein in GSPP also showed strong inhibition on the proliferation of hepatocarcinoma Bel-7402 cells [34].

Many researches have revealed the strong anticancer activity of berberine. The protective effects of berberine on liver diseases including liver cancer have been widely studied by our groups. The quaternary ammonium salt derived from Coptidis Rhizome (Huanglian in TCM) can induce both autophagy and apoptosis in hepatocellular carcinoma cells (HCC). Further mechanisms studies demonstrated that berberine could induce mitochondrial apoptotic signaling pathway in MHCC97-L and HepG2 cells via upregulating Bax expression. Furthermore, berberine could also induce autophagic cell death in HCC cells through inhibiting the activity of Akt and activating the p38 MAPK-signaling pathway [35].

4.2. Chinese medicines and their active compounds for inducing liver cancer cells differentiation

Panaxydol is one of the bioactive components in Panax Notoginseng (Sanqi in TCM). Panax Notoginseng is a famous hemostatic in TCM and it can also relieve other blood disorders, such as blood stasis or blood deficiency. Recent studies have shown that the panaxydol could induce cell differentiation in human HCC cell lines SMMC-7721 [36]. Ultrastructure morphology observation confirmed that there have obvious cell morphologic changes after panaxydol treatment. The activity of several differentiation related proteins such as alkaline phosphatase and albumin were increased, while AFP activity was significantly decreased after panaxydol treatment. These results showed that panaxydol may be a potential antihepatoma agent by inducing tumor cell differentiation.

Gepsin can also inhibit liver cancer development by inducing cancer cells differentiation. Studies showed that after gepsin treatment, the HCC cell line Bel-7402 presents ultrastructural morphology of differentiation. Western blot results revealed that the differentiation related proteins such as the AFP protein secretion significantly decreased, while ALB protein expression was obviously up-regulated on gepsin-treated cancer cells [34].

Ginseng is one of the most widely used herbs in TCM for thousands of years. Ginsenosides are the main bio-active components in Ginseng. There are many reports verified the anticancer effect of ginsenosides *in vitro* and *in vivo*. For example, ginsenosides-Rh2 (G-Rh2) can inhibit the proliferation of SMMC-7721 cells as well as induce the mature and normality of cell ultrastructure morphology. The expression of AFP, gamma-GT and heat-resistant ALP were also significantly decreased after 10 mg/ml G-Rh2 treatment [37].

4.3. Chinese medicines and their active compounds for averting the invasion and metastasis of liver cancer cells

Ardipusilloside I is a triterpene-saponin separated from the TCM herbs *Ardisia pusilla* A. DC. Recent studies have revealed its anticancer effects through inhibition invasion and metastasis of HCC cells [38]. Both *in vitro* and *in vivo* studies demonstrated that Ardipusilloside I may suppress migration of HCC cells partially by decreasing the expression of the metalloproteinase (MMP)-2 and MMP-9 proteins. In addition, Ardipusilloside I can activate Rac1 protein and further induce E-cadherin which may result in inhibition of cancer cells migration.

As we have discussed earlier, GSPP and its monomeric protein gepsin are effective in inhibiting the proliferation of HCC cells. Recent studies found that GSPP was also effective in suppressing the migration of HCC cells [33]. GSPP treatment remarkably decreased the concentration of intracellular calcium. Many studies have demonstrated that low intracellular calcium concentration is associated with reduced cancer migration. GSPP treatment could remarkably decrease the concentration of intracellular calcium. Thus, the antimigration effect by GSPP may be partially a consequence of downregulation of intracellular calcium concentration together with an upregulation of actin filaments polymerization in HCC cells.

The hepatic protective effects of Radix Salviae have been verified through its extensive use in TCM. Recent studies also found that aqueous extracts of Radix Salviae can inhibit the devel-

opment of liver cancer by suppressing the metastasis and recurrence in animal models [21]. *In vitro* study showed that Radix Salviae treatment significantly decreased the expression of Intercellular Adhesion Molecule 1(ICAM-1) in SMMC-7721 cells. In addition, it could suppress the invasion of SMMC-7721 cell and make the fibronectin-attached cells exfoliated. The cell adhesion ability of HCC-HCC, HCC-lymphocyte and HCC-endothelial cell also decreased after Radix Salviae treatment. The tumor xenograft mice model also confirmed the antimetastasis effects of Radix Salviae on posthepatectomy liver cancer *in vivo*.

Curcumin, a polyphenol isolated from the rhizome of Curcuma longa (Jiang in TCM) has potential anti-cancer effects in many types of cancers. However, due to its poor aqueous solubility, the clinical application of curcumin has been limited. A recent study has used the polymeric nanoparticle formulation of curcumin to improve its solubility as well as anticancer activity [39]. The results showed that when used as a combination with sorafenib, the modified curcumin can suppress the proliferation and invasion of HCC cells *in vitro*. Furthermore, *in vivo* study also found curcumin could inhibit liver cancer growth and lung metastases. Mechanisms study found curcumin and sorafenib synergistically inhibited the expression of MMP9 by down-regulating NF-kappaB/p65-signaling pathway. Taken together, the polymeric nanoparticle formulation of curcumin may exhibit antitumor activity by inhibiting liver cancer metastasis.

4.4. Chinese medicines and their active compounds for inhibiting angiogenesis in liver cancer treatment

Angiogenesis is a physiological process during which new blood vessels are produced and developed based on the original vessels. As angiogenesis plays a crucial role in tumor growth and metastasis, the novel antitumor therapies targeting angiogenesis may provide new hopes for cancer treatment. Livistona Chinensis seeds (EELC) have been used for centuries in TCM for cancer treatment. HCC xenograft mice model confirmed that EELC can inhibit tumor angiogenesis through the Notch-signaling pathway [40]. After EELC treatment, *in vivo* results showed remarkable decrease in intratumoral microvessel density (MVD) in the HCC xenograft mice tumors. In addition, the angiogenesis-related proteins such as the VEGF-A and VEGFR-2 were significantly decreased after EELC treatment. The mechanism study demonstrated that the antiangiogenesis effect was related with the inhibition of the Notch pathway as the expression of Notch, Dll4 and Jagged1 were down regulated according to the real-time polymerase chain reaction (RT-PCR) results.

Yang Zheng Xiao Ji (YZXJ) is a commercial TCM product for supplementary treatment of advanced liver cancer. Some clinical trials indicated that YZXJ may improve the curative effect of interventional chemotherapy for advanced liver cancer patients. *In vitro* studies showed that YZXJ can inhibit the matrigel-based sandwich tubule formation and cell migration. Western blot results confirmed that inhibition of the activation of focal adhesion kinase may at least in part confer the YZXJ-induced inhibition of cell migration and tube formation [41]. These results indicated that YZXJ could be a potential antihepatoma TCM product via suppressing tumor angiogenesis.

Asparagus polysaccharide, the bioactive derivate from Asparagus, is a common TCM herbal diet that may exhibit anticancer activity according to previous researches. One study has explored the adjunctive effects of asparagus polysaccharide in liver cancer chemotherapy [42]. Their results showed that asparagus polysaccharide significantly suppressed liver cancer growth in combination with transcatheter arterial chemoembolization (TACE) therapy in orthotopic HCC rat model. Tumor angiogenesis may be the major target for asparagine gelatinous in liver cancer treatment. Several angiogenesis markers such as CD34 and VEGF significantly decreased after asparagine gelatinous treatment. The expression of MVD markers also remarkably reduced in asparagus polysaccharide treated liver tumors. These results suggested that asparagus polysaccharide with TACE could apparently inhibit the tumor angiogenesis *in vivo*; asparagus polysaccharide might be a potential adjunvant therapy for TACE in treating liver cancer.

4.5. Chinese medicines and their active compounds for enhancing immunological function in liver cancer patient

The TCM formula Songyou Yin (SYY) was developed by Professor Zhao-You Tang for liver cancer treatment. Recent studies have found that the antimetastasis and anti-recurrence effects by SYY may be correlated with its immunomodulation activity. SYY can significantly extend survival and inhibit the tumor growth and metastasis in tumor-burdened mice. SYY remarkably increased the ratio of CD4/CD8 in peripheral blood and decreased the serum TGF-beta1 activity as well as the percentage of Treg cells both in spleen and peripheral blood. Thus, the TCM product SYY may strengthen the immunity of liver cancer patient and prevent tumor recurrence [43].

Mylabris mixture is a popular anticancer TCM formula which mainly consists of the Mylabris extracts, Tangerine Peel and Millet Sprout. Recent studies found that Mylabris mixture could obviously suppress the growth of liver cancer H22 cells by improving the immunological function in mice model [44]. After Mylabris mixture treatment, the stimulation index of T-lymphocyte transformation and proportion of NK cells were apparently increased. The subpopulation percentage of T lymphocytes also significantly increased after Mylabris mixture treatment. Up-regulation on the secretion of interferon-gamma and interleukin-4 by T lymphocytes also confirmed the immunoloregulation effects by Mylabris mixture.

A recent study has explored the immunoloregulation effects of ultrasound-guided intratumoral injection of TCM formula "Star-99" in HCC in mice model. Star-99 can improve the cellular immunity and induce HCC cell apoptosis by increasing the level of plasma IL-2 and TNF-alpha. The cytokines IL-2 can be considered as an immunological response modifier. It can improve the activity of lymphocyte and the anti-tumor effects of NK, CTL and LAK cells as well as cytokine secretion. In addition, another experiment also found that many lymphocytes can be observed in the tumor tissues after the Star-99 treatment [45]. The electron microscope results observed that the microvilli on the surface of the lymphocytes attacked the cancer cells. The membrane of tumor cell in contact with the sensitized T lymphocyte became broken with the organelle and the nucleus dissolved and the vacuolation of the cytoplasm as

well. This phenomenon further illustrate that the Star-99 could stimulate and induce the cellular immunity function of the organism.

Previous studies revealed the TCM herbal product Kanglaite (KLT) which mainly consists of Jobstears Seed oil exhibits anticancer and immunoregulation activities. According to a clinical study, KLT treatment can improve the immunological function via increasing the proportion of T cells and NK cells in the blood of HCC patients [46]. *In vivo* study in tumor-bearing mice showed that KLT enhanced the immune system by increasing the secretion of several cytokines such as the IFN-gamma and IL-2, and up-regulate the proportion of CD4+ T cells in mice. These events further improved the killing activity of NK cells and CD8+ T cells against the HepG2 cells. KLT treatment also up-regulate the mRNA level of some NF-kappaB responsive genes in CD4+ cells. In conclusion, KLT may have immunomodulatory activity at least partially through the activating of NF-kappaB mediated gene transcription in CD4+ T cells.

4.6. Chinese medicines and their active compounds for reversing drug resistance in liver cancer treatment

Astragaloside is a saponin isolated from Radix Astragali, one of the popular TCM herbs. Astragaloside has been reported to be an effective agent in reversing multidrug resistance (MDR) of cancer treatment. A recent study found that astragaloside can modulate the expression of P-glycoprotein in human hepatic cancer cells Bel-7402 and reverse 5-fluorouracil resistance in chemotherapy. As P-glycoprotein majorly is responsible for the drug efflux in cancer treatment, the down-regulation of P-glycoprotein will inhibit P-glycoprotein-mediated drug efflux and improve the efficacy of chemotherapies [47]. Thus, astragaloside may be a potential anticancer drug for reversing drug resistance in liver cancer treatment.

Polyphyllin D is a saponin derived from a TCM herb Paris Polyphylla. The herb of Paris Polyphylla has been used for liver cancer treatment in China for thousands years. Previous study showed that polyphyllin D can induce apoptosis in multi-drug resistant HepG2 cells [48]. Further mechanism study demonstrated that polyphyllin D may elicit mitochondrial fragmentation in HCC cells. When treating polyphyllin D directly to the isolated mitochondria, the mitochondria exhibited strong swelling with deep transmembrane depolarization. In addition, significant apoptosis-inducing factor release could be observed from the multidrug-resistant HepG2 cells. These results suggest that polyphyllin D may be a potential anti-cancer agent targeting drug resistance in HCC cells by inducing mitochondrial damage.

Piper betel leaves (PBL) are enriched with medication properties in TCM for many centuries. Modern researches have proven that PBL has antioxidation activity and may inhibit gene mutation. Recent study has found that PBL extract can inhibit total Glutathione S-transferase (GST) and alpha class of GST (GSTA) in HepG2 cells [49]. Further study showed PBL could enhance the sensitivity of HCC cells to chemotherapy. The results revealed that the cytotoxicity of cisplatin was apparently increased in cell with PBL treatment, with the mechanism related to the inhibition of multidrug resistance protein 2. These results indicat-

ed that PBL extract may reduce drug resistance and improve the efficacy of chemotherapy in liver cancer treatment.

5. Future prospect of liver cancer treatment by Chinese medicines and their active compounds

CMs and its active compounds have a long history for anticancer treatment in China. In recent decades, many TCM formulae, herbal extracts or isolates have been developed to treat liver cancer, especially for patients with advanced-stage liver cancer. According to both clinical studies and basic researches, CMs have less toxicity and exhibit multitarget anticancer activity. In China, the antihepatoma effects of several TCM products have been verified by clinical trials, such as the Songyou Yin and Kanglaite injection. Many studies have proven that CMs had beneficial effects in relieving fatigue and pain, preventing respiratory tract infections and alleviating gastrointestinal symptoms in liver cancer patients.

However, there are also some problems with CMs in current cancer treatment that should be considered seriously. First of all, most of the CMs are extracted from plants or animals, their pharmacological active components are still unknown CMs. Second, the adverse effects, contraindications and corresponding clinical data of CMs are rarely indicated by TCM doctors or CMs manufacturers. Third, the frequent occurrence of fatal accidents such as allergy and phlebitis has been observed during TCM treatment especially in TCM injection treatment. Finally, although there are many clinical trials on CMs for liver cancer treatment, none of them were large multicenter trials with strict and standard criteria CMs. In this case, it is difficult to give an accurate conclusion about the effects of CMs for liver cancer treatment when conducting a meta-analysis. Therefore, large-scale multicenter clinical trials with strict and standard criteria are urgently needed for the development of TCM in liver cancer treatment. According to the previous studies, combination of CMs and its active compounds with surgery, TACE or chemotherapy may protect liver function, enhance the patients' immune response, and reduce the side effects and complications of conventional therapy as well as prolong lifespan. With the rapid development of modern scientific research, the combination therapy with TCM will be definitely promising for future liver cancer treatment.

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