Chapter 7

What Chinese Medicine Can Do for Liver Cancer?

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Additional information is available at the end of the chapter

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Abstract

Liver cancer is an international problem, especially in Asian countries. It is because that most liver cancers are already late stage when they are diagnosed, and also most liver cancers have various previous chronic liver diseases induced by alcoholic, virus, and steatosis, etc. In recent years, laboratory and clinical studies focusing on liver cancer by Chinese medicine has been extensively studied. What Chinese medicine treatment formalities can be used in liver cancer? How Chinese medicine can be employed in treatment of liver cancer? What Chinese medicine can contribute to liver cancer? To answer these questions in this chapter, we will review and discuss treatment of liver cancer from Chinese medicine's perspective with scientific evidences as following three parts: (1) Chinese medicine as the source of discovering new treatment for liver cancer, (2) Chinese medicine as a complementary treatment of liver cancer, and (3) to discuss future research and application of Chinese medicine in liver cancer treatment.

Keywords: Chinese medicine, liver cancer, source of drug discovery, complementary medicine, clinical application

1. Introduction

Liver cancer is one of the most common malignancies with high morbidity and mortality all over the world. Despite the number of new cases of liver cancer appears to be plateauing, large population size of liver cancer patients, especially in China, still greatly contributes to the global cancer deaths [1]. Hepatocellular carcinoma (HCC) is the most commonly observed histological subgroup of primary liver cancer, accounting for 70–90% of the cases. With a global status quo that 746,000 deaths only in 2012 and 10.1 new cases diagnosed within every 10,000 people, HCC ranks the sixth lethal malignancy and the third leading cause of cancer-related deaths [2].

Over the past decades, the clinical approaches to treat liver cancer have considerably evolved. Patients can benefit from partial hepatectomy, radiotherapy, systemic or local chemotherapy, liver transplantation, and radiofrequency ablative surgery. Nevertheless, numerous adverse events and dismal outcomes still seriously affect the life quality of patients. On the background of shortcomings, developing improved preventive and therapeutic strategy is urgently necessary.

Considering its low toxicity and high activity, Chinese medicine has been deemed as one of the prominent complementary and alternative approaches in tumor therapy. As unique biomedical and pharmaceutical resources, Chinese medicine owns the ability of providing better treatment for liver cancer, either alone or in integrative way [3]. According to Hong Kong Liver Cancer staging system in a population-based investigation, for patients with Va/Vb (tumor status being early, intermediate or locally advanced), the most frequent treatment was Chinese medicine [4]. Another cohort study in Taiwan reported that Chinese medicine users exhibited significant lower risk to suffer HCC, which supported the application of Chinese medicine into the clinical practice of liver cancer treatment [5]. A recent meta-analysis showed that add-on therapy with Chinese medicine regimens in HCC could reduce side effects, activate tumor responses, and improve overall survival. Moreover, cancer subjects were reported to be more inclined to integrating Chinese medicine regimens with conventional therapies rather than conventional treatment only [6]. In this regard, Chinese medicine has been considered as a potential curative choice of method for controlling the proliferation of liver cancer, and thus improving the quality of life and prolonging overall survival of the patients.

Historically, the medical foundation of Chinese medicine can be traced back to 5000 years ago. With contributions and dedications of Chinese medical people in modern and old times, Chinese medicine has been gradually evolved and accepted by the mainstream society. In particular, accompanying the tide of Chinese immigration and cultural communication, Chinese medicine has been approved worldwide and employed in clinical practice in at least 183 countries [7]. Even though many regions have the regulations imposing restrictions to ensure that Chinese medicine is beneficial to liver cancer patients instead of being harmful to public health, the evidence-based guideline has not been covered every field [8, 9].

However, due to its effective curative outcomes in real life, the usage of Chinese medicine in various forms of single compounds, extracted fractions, and composite formulae has attracted a great deal of attentions over the past few decades. Chinese medicine may be capable of retarding liver cancer progression with its multitargets and coordinated intervention actions, either in combination with conventional therapies or radiation alone. Here, we retrospectively reviewed and analyzed the functional roles of Chinese medicine in the treatment of liver cancer.

2. Chinese medicine as the source of discovering new treatment for liver cancer

As mentioned above, currently there are various therapies for liver neoplasm. However, the overall survival rate of patients still remains unsatisfactory on account of high invasiveness

and metastasis, chemotherapeutic resistance, and so on. Chinese medicine, in various forms including composite formulae, extracted fractions, monomers, and their derivatives, has been pursued as ideal and novel sources for therapeutic agent development for cancer.

2.1. Single compounds from Chinese medicine for the treatment of liver cancer

Berberine is a natural product in many Chinese medicinal herbs, especially *Coptidis rhizoma*, which has been extensively studied and reported to show the antitumor action mostly by modulation of a number of different signal transductions. Currently, scholars have explored the antitumor action of berberine in liver cancer by various different strategies. For instance, in our laboratory, we found that berberine-induced cell death and tumor growth inhibition in xenograft model were demonstrated and mechanism was revealed that miR-23a might play a mediated role in berberine-suppressing HCC growth [10]. Also, cyclin D1 overexpression is mainly responsible for tumor expansion, metastasis as well as angiogenesis. Berberine was found to repress the expression of cyclin D1 via proteasomal degradation in HCC [11]. In addition, our group identified that berberine exerted antimigratory and anti-invasive abilities in HCC cells involving the upregulation of PAI-1 and downregulation of uPA [12]. On the other hand, our group described for the first time that berberine could trigger autophagic cell death, in which the compound was shown to activate Beclin-1 and suppress mTOR [13]. Actually, lung metastases in liver cancer are also a serious problem for patients, and we identified that the anti-invasive and antiproliferative actions of berberine in liver cancer was at least in part involved in the downregulation of Id-1, revealing a new anti-invasive mechanism [14]. Hence, berberine is predicted as a new and potent natural molecule targeting liver cancer.

Flavonoids commonly exist in Chinese medicine and could be isolated from many different kinds of herbal medicine. In recent years, the precise molecular mechanism underlying the obvious antiliver tumor effect of flavonoids has been studied. For example, hydroxysafflor yellow A (HSYA), a kind of flavonoid extracted from *Carthamus tinctorius* L. owns the ability of antitumor. It was demonstrated that HSYA could result in angiogenesis inhibition of HCC by blocking signaling pathways of ERK/MAPK and NF-κB in comparison with negative control group. More interestingly, spleen and thymus indexes have been demonstrated to be improved, suggesting improvement on the immune system by HSYA [15]. Oroxin B (OB) is one of the flavonoids isolated from *Oroxylum indicum* (L.) Vent. Li et al. investigated the antitumor effects of OB on HCC cell line SMMC-772 and studied the underlying mechanisms by which OB markedly inhibited expansion and induced apoptosis of the HCC cells. The antitumor activity of OB probably involved the inhibition of COX-2/VEGF and PTEN/PI3K/AKT signaling pathways, providing evidence for OB being used as a new therapeutic agent for liver cancer [16]. Another flavonoid, namely luteolin, showed antineoplastic activity in a number of cancer cells. In SMMC-7721 HCC cells, luteolin induced apoptosis partially via modulation of autophagy, indicating luteolin serving as a regulator of autophagy in treating liver cancer [17].

Brucein D (BD) is an active constituent derived from *Brucea javanica* fruit, which has been employed as an antitumor recipe in Chinese medical practice. It was revealed that BD exerted observable apoptotic induction in HCC in vitro and in vivo, which was attributed to the reduced expression of miR-95 [18].

Matrine, a chemical component came from the roots of sophora species, mainly *Sophora flavescens* Ait (SF), has been used clinically to treat diseases such as liver fibrosis. The hepatospecific *miR-122a* has been found decreased in HCC cell lines [19]. Zhou et al. reported that in HepG2 cells, matrine could cause cell arrest alteration as well as apoptosis induction with recovering expression of miR-122a [20]. Actually, matrine is the prominent bioactive compound in one adjuvant treatment of liver cancer, namely Fufang Kushen injection, which was approved by Chinese FDA in 1995. Matrine has been deemed as the favorable lead source for drug discovery owing to its changeable structure and stable safety profile. Researchers designed and synthesized a group of matrine derivatives, which improved the antitumor activities of matrine in several human cancer cell lines. Among four tested cell lines, HCC cell line Bel-7402 responded more sensitively to compounds than the other three cell lines. Matrine and its derivatives induced G1 cell cycle blockage as well as migration inhibition in HCC cells [21]. Another matrine derivative named WM622 showed remarkable inhibitory effect on HCC both in vivo and in vitro. Further study showed the apoptotic induction, cell cycle blocking in G0/G1 phase and the inhibition of PI3K/AKT signaling were involved in the antiliver cancer effect of WM622 [22].

Longikaurin A (LK-A) is a naturally occurring compound of ent-kaurane obtained from *I. aternifolius*. Researchers explored LK-A administration in liver of tumor-bearing mice models and discovered that LK-A could induce cell cycle arrest at G2/M phase with downregulation of Skp2 and subsequently resulted in induction of ROS/JNK/c-Jun apoptotic pathway in HCC cells [23].

The antitumor of two known pennogenyl saponins, which are derived from *R. paridis axialis*, was investigated in orthotopic nude-mouse model. The data indicated that these two monomers dose dependently suppressed the HCC progression through activating both caspase-independent and caspase-dependent apoptotic pathways. Furthermore, possible mechanism probably involved the modulation of mitogen-related protein kinase pathway as well as the suppression of PI3K/Akt signaling [24].

Isoquercitrin was found to strongly repress liver tumor cells via retarding the G1 phase cell cycle and promoting cancer cells apoptosis. In nude mice, the proliferation of transplanted tumors was suppressed after treatment with isoquercitrin. Further study showed that the underlying mechanism might be closely involved in the MAPK and PKC signaling pathways [25].

Zhang et al. investigated the effect of astragaloside IV (AS-IV) and curcumin on tumor expansion and angiogenesis in nude mice bearing xenografts of HCC. Combining AS-IV and curcumin revealed significant synergistic repressive efficacy against both angiogenic and thrombosis-related factors, which might be mediated by downregulation of *miR-221* as well as upregulation of *miR-122*. This current study indicated future clinical potential of combination therapy with AS-IV and curcumin for treatment of liver cancer [26].

Ursolic acid (UA), a naturally occurring pentacyclic triterpenoid carboxylic acid found among Chinese herbal medicine, has been reported to be a potent component for cancer prevention, including liver cancer. Yie et al. explored the probable mechanisms underlying the antiliver cancer action of UA. Taken together, the results demonstrated that UA inhibited proliferation

and induced apoptosis of HCC cells via AMPKα-mediated suppression of Sp1, followed by suppressing DNMT1 expression. The investigation revealed a potential novel mechanism by which UA controlled proliferation of HCC cells, suggesting the critical effect of DNMT1 in HCC chemoprevention and treatment [27].

Bilobol is a Chinese medical ingredient. Xu et al. identified that bilobol administration could suppress expansion of HepG2 cells, which pretreated with lipopolysaccharide (LPS) to induce inflammation. Bilobol appeared to exhibit antitumor effect via inhibiting the RhoA/ROCK signal transduction during the anti-inflammatory response [28].

Fucoidan, a sulfated polysaccharide isolated from brown algae, has been applied as an anti-cancer drug for hundreds of years in Chinese medicine. The results from Zhu et al. revealed that fucoidan had the capacity of antitumor partially through inhibiting the proliferation of HCC cells, although it is unable to repress the angiogenesis induced by HCC [29]. In another study, fucoidan displayed the antimetastatic efficacy on HCC cell lines via upregulating p42/44 MAPK-dependent NDRG-1/CAP43 pathway. Also, fucoidan was found to protect against bile acid-induced hepatocyte apoptosis. This ability suggested fucoidan presented a potent therapeutic agent for HCC treatment [30].

Telekin is a eudesmane-type sesquiterpene lactone extracted from the natural plant *Carpesium divaricatum*, which presents strong antiproliferative activity in cancer cells. Zheng et al. found that telekin promoted HCC cells apoptosis by activating the mitochondria-mediated apoptotic pathway [31].

Gigantol is a phenolic substance derived from the genus Dendrobium. Chen et al. investigated gigantol efficacy on liver cancer cells and the results suggested gigantol inhibited cells expansion and induced apoptosis in HepG2 cells through PI3K/Akt/NF-kappaB signal transduction [32].

The endoplasmic reticulum (ER) stress and unfolded protein response (UPR) play critical roles in the modulation of cell fate. The two factors even could become potent targets and provide support for the development of antineoplastic agents. Celastrol, one of the triterpene compounds derived from herbal medicine, exerts antitumor effects on various malignancies. Ren et al. demonstrated that for HCC cells, exposure to celastrol led to the sensitivity of the intrinsic apoptotic pathway, at least partly through ER stress and the UPR. Moreover, celastrol was found to repress H22 tumor growth in murine syngeneic model studies by inducing ER stress and apoptosis. These data suggested that targeting ER-stress/UPR was an efficient way for celastrol becoming a potent drug for HCC therapy [33]. Cytisine, a quinolizidine alkaloid, also a major bioactive constituent purified from the *Sophora alopecuroides* L. It was reported to exhibit inhibitory effects in treating liver cancer by inducing the ER stress-mediated apoptotic pathway through activating CHOP, JNK, and caspase-4 signaling pathways in liver cancer cells. This phenomenon suggested a novel target compound potentially to treat liver cancer [34].

RA-XII, a naturally occurring compound originated from Chinese herbal medicine Rubia yunnanensis, possesses activities of anti-inflammatory and antitumor. Song et al. revealed that RA-XII accelerated apoptosis and repressed protective autophagy via signaling pathway AMPK/mTOR/P70S6K in HepG2 cells, suggesting RA-XII, a cyclopeptide, provides the therapeutic support for potentially being an autophagy inhibitor drug in the therapy of hepatic tumor [35].

There are many bioactive compounds from Chinese medicine, which are also one part of daily diet. For example, *Bullacta exarata* is widely used as a part of normal diet in Asia, and also it is an agent with liver- and kidney-nourishing functions. One polysaccharide conjugate BEPS-IA was extracted from *B. exarata*. Liao et al. reported that BEPS-IA exerted a potent inhibition in HepG2 cells growth in a concentration-dependent manner via inducing apoptosis and blocking cell cycle. Furthermore, it was corroborated that this effect was involved in downregulation of Bcl-2, upregulation of p53, p21 and Bax, suggesting that BEPS-IA may be a new dietary drug for HCC obtained from herbals and shed light on getting a deeper understanding on the action mechanisms [36]. Diosgenin is a major bioactive component of Dioscoreaceae plants including yam, which is commonly prescribed in Chinese medicine, and a common vegetable all over the world. Diosgenin remarkably repressed the proliferation of several HCC cell lines in a dosage-dependent manner. Deeper investigation reported the apoptosis and cell cycle G2/M arrest were involved in the inactivation of Akt, activation of the caspase cascades, and upregulation of p21 and p27 expression. These results suggested that diosgenin may serve potentially as a novel antiliver cancer dietary supplement [37]. *Armillaria mellea* (*A. mellea*) is a honey mushroom, which is currently often consumed worldwide as a dietary supplement. Armillarikin was purified from *A. mellea*, which is an important component of Chinese medicine "Tianma." Chen et al. investigated the cytotoxicity of armillarikin against HCC cell lines such as Huh7, HA22T, and HepG2 cells. Armillarikin treatment induced apoptosis that was mediated by ROS and accompanied by the collapse of mitochondrial and activation of caspase-8 and -3 in cancer cells, suggesting the potential of armillarikin serving as an potent antihepatoma drug [38]. Corosolic acid analogue (CAA) is a triterpenoid saponin isolated from *Actinidia valvata* Dunn (Actinidiaceae), a kind of well-known fruit. The study investigated the antiproliferation and inducing apoptosis effects of CAA in three hepatoma cell lines. The data showed for the first time that CAA inhibited expansion of liver cancer cell lines and induced G1 phase arrest. Moreover, proapoptotic effect of CAA was mediated by the activation of TNF-α, caspases, and mitochondrial pathway [39].

1,6,7-trihydroxyxanthone (THA) is an active small molecule purified from *Goodyera oblongifolia.* The compound was discovered to strongly inhibit cancer cell proliferation and induced apoptosis in hepatoma carcinoma cells partially mediated by the repression of Bmi-1 and activation of miR-218 [40].

An active ingredient cordycepin was extracted from "Dong Chong Xia Cao." It has been implicated in regulating multiple physiological actions especially antitumor effects. Yao et al. revealed that cordycepin might contribute to tumor progression, EMT, migration, and invasion inhibition in HCC by suppression of signaling pathways E-cadherin and integrin/FAK. Hence, cordycepin is a supplementary candidate or therapeutic agent for preventing liver tumor expansion [41].

Norcantharidin (NCTD), a small-molecule antitumor drug originated from small animal *blister beetle*, has been currently applied as a potent antineoplastic agent for several kinds of cancers including HCC. The expression of FAM46C, which has been firstly reported as a tumor suppressor for multiple myeloma, was demonstrated to enhance with NCTD administration. FAM46C, a tumor inhibitor for HCC, was important for proapoptotic effects and antiproliferation of NCTD

[42]. Another study investigated the mechanism of NCTD-induced apoptosis in HepG2 cells, which indicated that NCTD could reverse the methylation state of RASSF1A gene and recover its expression, providing the theoretical information for further development in clinical application [43]. Also, Zhang et al. found in multiple HCC cell lines that NCTD could induce transcriptional repression of Mcl-1 and significantly enhance ABT-737-triggered cell viability inhibition and apoptosis [44].

Bufalin is the major bioactive constituent of the Chinese medicine Chansu, which is presently employed in clinical practice for cancer therapy. A number of groups have investigated the therapy efficacy of bufalin on hepatoma, either in vivo or in vitro, to explore the therapeutic potential of the drug. Qiu et al. reported that bufalin exhibited considerable antitumor activities in liver cancer cell lines HCCLM3 and HepG2 and the underlying mechanism might be related to the repression of signaling pathway AKT/GSK3β/β-catenin/E-cadherin [45]. Tsai et al. demonstrated that bufalin led to autophagic cell death and G2/M cell cycle phase arrest in SK-HEP-1 HCC cells via activating AKT/mTOR signal transduction pathway [46]. Another group reported that bufalin exerted remarkable antiproliferative activity and apoptosis induction in Huh-7 and HepG-2 cancer cells. Further study supported the prosurvival role of bufalin-induced autophagy when the autophagy pathway was retarded with specific chemical inhibitors, indicating a promising therapeutic approach for HCC therapy combining bufalin with a specific autophagy inhibitor [47].

In searching for active antihepatoma ingredients from *toad venom*, which is a frequent prescription applied in HCC treatment, Zhang et al. discovered that arenobufagin, a bufadienolide derived from toad venom, had prominent anticancer capacity against HepG2 cells and the corresponding multidrug-resistant cells, namely HepG2/ADM. They illuminated the molecular mechanisms of arenobufagin, which involved crosstalk between autophagy and apoptosis through PI3K/Akt/mTOR pathway suppression. Consequently, these findings contributed to the development of arenobufagin into a chemotherapeutic agent in liver cancer treatment [48]. Another compound, namely hellebrigenin, which was also isolated from *Venenum bufonis*, was found to significantly repress HepG2 cell viability and colony formation. Further exploration revealed the cytotoxicity of hellebrigenin in HepG2 cells and underscored the antihepatoma activity of hellebrigenin as an active component of *Venenum bufonis*. Hellebrigenin induced DNA damage, triggered cell cycle arrest, and subsequently initiated mitochondrial apoptosis. Moreover, Akt was found to take a role in cell cycle and apoptosis modulation induced by hellebrigenin. The findings showed the potential of hellebrigenin used as a chemotherapeutic drug for future HCC clinical application [49].

2.2. Functional roles of Chinese medicine extracts and fractions in liver cancer

Asparagus is not only consumed in daily diet but also employed as an agent in Chinese medicine for multiple types of malignancies therapy. An extract from asparagus, asparagus polysaccharide, has been confirmed to be the major bioactive constituent of asparagus in the respect of antitumor as well as immunity-enhancing activities. In clinical practice, it has been used in a number of malignancies treatment [50]. Weng et al. applied tumor-bearing rat model to systemically evaluate the toxicity and antitumor activity of asparagus polysaccharide and

asparagus gel-like material. The results showed a certain tumor inhibitory effect of them via promoting cell apoptosis and suppressing tumor angiogenesis when given as transarterial chemoembolization (TACE) therapy. Meanwhile, it exerted the antihepatoma activity with lower toxic effects as well as reduced kidney and liver functional damage, highlighting its chemotherapeutic potential in clinical application for future liver cancer TACE therapy [51].

Ganoderma lucidum polysaccharides (GLPS) have been exploited as folk Chinese medicine for their properties of immunomodulation and tumor prevention [52]. Li et al. measured the efficacy of GLPS on liver cancer cells in hepatoma-bearing mice model and effectively suppressed the tumor growth. The possible molecular mechanism may be related with an augment of the ratio of regulatory T cell (Treg) to effector T cell (Teff), which is caused by the augment of miR-125b, a predicative marker of poor prognosis and aggressiveness of liver cancer [53].

In China, *Trametes robiniophila Murr* (Huaier) has recently been used as Chinese medicine in China. It has a great clinical effect as adjuvant therapies in the treatment of HCC. Shan et al. investigated the functions of Huaier on HCC cells and confirmed that HCC growth could be restrained by Huaier through downregulation of yes-associated protein 1 (YAP1) [54].

Ampelopsis sinica root (ASR) is a well-known hepatoprotective Chinese medicine. Wang et al. explored whether ethyl acetate extract from ASRE had the antihepatoma activity both in vitro and in vivo. The findings showed that ASRE had prominent antihepatoma activity, which possibly involved the decreased regulation of inflammatory cytokines such as cyclooxygenase-2, 5-lipoxygenase and FLAP, augment of p53 protein expression and the ratio of bax/bcl-2, caspase-3 activation, as well as survivin repression. Moreover, ASR was found to be nontoxic on normal cells, suggesting that it may serve as a potential therapeutic agent for HCC treatment [55].

An extract of *Stellerachamaejasme* L. (ESC) had been confirmed as a potential antitumor extract of Chinese medicine. Liu et al. tested that the suppressive effects of ESC on propagation and epithelial mesenchymal transition (EMT) in liver cancer cells were associated with miR-107. The findings indicated ESC retarded HCC expansion and metastasis by regulating the expression of microRNAs and their according target genes [56].

Cnidium monnieri (L.) Cusson (CME) is a frequently used Chinese herbal medicine that treats gynecological diseases and carbuncles. A recent study showed the cell cycle alteration and apoptosis of HepG2 (wildtype p53) and Hep3B (p53null) by ethanol extract of CME, suggesting that CME induced G1 arrest and apoptosis via the Akt/GSK3β signaling pathway [57].

Astragalus membranaceus and Salvia miltiorrhiza are medical plants that have been applied for thousands of years in the treatment of liver diseases. According to previous researches, it has showed that these two herbs and their extracts own the ability to inhibit the development liver cancer. Rui et al. investigated that the compound astragalus and salvia miltiorrhiza extract (CASE) could repress diethylinitrosamine-induced hepatoma in rat model via the inhibition of fibrosis and PAI-1 mRNA transcription, indicating the possibility of being development as antihepatoma agents in preventing and treating human liver cancer [58].

Salvia chinensis Benth has been traditionally exploited for several centuries since old times to treat malignant diseases including HCC. In a study, total flavonoids isolated from *Salvia chinensis* Benth were shown to own the capability of inducing HCC cell apoptosis both in vitro and in vivo, which appeared to be implicated in the suppression of NF-κB activity [59]. *Coptidis rhizoma* has been used in clinical practice for tumor treatment in Chinese medicine, and recent experiments in our laboratory have supported its employment in tumor treatment. Zhu et al. examined the anticancer efficacy of *Coptidis rhizoma* aqueous extract (CRAE) on HCC cells and found the alterations of miR-21 and miR-23a after treatment with CRAE. The results suggested that CRAE targeted the miRNAs in hepatoma cells [60]. Wang et al. found that CRAE could remarkably downregulate Rho/ROCK signal transduction, then finally interfere MHCC97-L cell migration [61]. As we know, angiogenesis is an important factor, which is beneficial for tumor expansion. Tan et al. confirmed that antiangiogenic effect of CRAE on HCC was partially dependent to an eEF2-driven pathway [62]. All these findings supported the potential application of CRAE in HCC therapy.

Prunella vulgaris (PV) is a small tree that has been employed clinically for thousands of years in Asia to treat herpetic keratitis. According to previous researches, it has showed PV could repress TPA-induced activation of MMP-9 and suppress hepatoma cells migration and invasion. Data suggested that by modulating multiple signaling pathways, PV modified the metastatic microenvironment of HCC. PV thus may provide useful information for systemic therapies of HCC [63].

Ethyl acetate extract (EAE) of *Euphorbia helioscopia* L. played a critical role in repressing tumor cell proliferation, apoptosis, invasion, and metastasis in vitro. Meanwhile, Cheng et al. found that change of expression of cyclin D1, Bcl-2, Bax, MMP-9 by EAE may be associated with inhibition of tumor growth, induction apoptosis, and suppression of tumor metastasis and invasion in HCC xenografts [64].

Some Chinese medicine scholars have indicated that endogenous wind-evil acted as a critical role in tumor metastasis. On the basis of this, the agent of dispelling wind-evil could serve as a suppressor for cancer metastasis and poor prognosis. Yan et al. observed that scorpion-medicated serum could restrain proliferation, induce apoptosis, as well as inhibit the capacity of migration and invasion in vitro. Further experiments in HCC tumor-bearing metastasis mice models showed that water decoction of scorpion blocked tumor growth and metastasis. More importantly, these results suggested that scorpion, as an important wind calming drug, could inhibit the metastasis and invasion of liver cancer cells especially through epithelial-mesenchymal transition (EMT) reversal, thereby providing a possible potential approach to preventing HCC metastasis [65].

Actinidia chinensis Planch root extract (acRoots) has been shown to inhibit cell proliferation in numerous cancer cells. Hou et al. used acRoots to treat HCC cells and observed the distinct effects of acRoots on cell proliferation, cell cycle arrest, and apoptosis. Furthermore, the mechanism underlying these activities was attributed to LAMB3-mediated proliferation suppression and S-phase cell cycle arrest in HepG2 cells [66]. He et al. studied the mechanism in

the extent of metabolic alterations. The data showed that acRoots could remarkably inhibit cholesterol metabolism through a PCSK9-mediated signaling pathway, which in turn limited the nutrients production that was essential for the proliferation of cancer cells [67].

Ethanol extract of root of *Prunus persica*, which is an important ingredient in Chinese medicine prescription, exhibited antitumor effect in liver cancer. Scholars recently reported that *Prunus persica* could repress cell growth in a time and dose-dependent fashion, causing sustained M/G2 phase arrest as well as notably suppressing the migration of HepG2 cells and the expression of extracellular matrix metalloproteases, MMP3 and MMP9 [68].

Realgar (As_4S_4), one of the most useful mineral drugs in Chinese medicine, has been employed in clinical therapy as a potential agent for cancer therapy. However, due to its low solubility and subsequent poor bioavailability, it is difficult to achieve the effective blood medicine dose unless with high dosage of realgar and long period of treatment. A recent study explored realgar transforming solution (RTS) and found the strong antihepatoma activity of RTS via inducing ROS [69].

2.3. The role of Chinese medicine composite formulae in regressing liver cancer

Huang-lian-jie-du-tang (HLJDT) is oriental medicinal formulation known to possess anti-inflammatory activity. The prescription has been well documented for thousands of years and used for liver protection in Asian community [70]. Recent researches have postulated HLJDT as a regimen for cancer treatment, particularly hepatoma. Hsu et al. found that HLJDT might have an effect on human liver cancer cell lines, Hep G2 and PLC/PRF/5. The results showed that HLJDT significantly triggered cell cycle arrest and contributed to the mitochondrial apoptotic pathway by reducing the level and activity of NF-κB, which suggested that HLJDT might be a promising chemotherapeutic agent without causing cytotoxicity to normal cellular environment [71]. Wang et al. examined the suppressive efficacy of HLJDT on the liver cancer expansion and found that involvement of eEF2 inhibition might be the key mechanism mediating the inhibitory effect of the formula [72].

Yiguanjian (YGJ), a classic liver-YIN tonifying herbal formula, was established by ancient Chinese medicine practitioner Wei Zhixian in the Qing Dynasty (AD 1722–1772). Researchers optimized the prescription of YGJ on the basis of modern principles in clinical practice of Chinese medicine and then evaluated the antitumor activity of modified YGJ (MYGJ) on Bel-7402 human liver cancer cells. These data showed that MYGJ could interfere proliferation suspension and induce anoikis in cancer cells. The mechanisms underlying the actions of MYGJ might involve in inhibiting the phosphorylation and expression of p38 MAPK, and subsequent regulating intrinsic and extrinsic pathways of apoptosis [73].

Pien Tze Huang (PZH) is an extensively employed prescription in the treatment of multiple malignancies and has possible therapeutic effects in clinical therapy for HCC. Qi et al. aimed to elucidate the efficacy of PZH on the proliferation and apoptosis of liver cancer cell lines and demonstrated PZH could effectively inhibit cancer cell proliferation and induce apoptosis in Bel-7402 HCC cells by upregulating miR-16, which has been verified as tumor suppressor, suggesting a novel potential therapeutic for HCC patients [74].

Sini-San (SNS) has been employed for the treatment of various types of liver disease. This formulation comprises four prescriptions of Chinese herbal medicine and was first described in "Shanghan Lun (Treatise on Cold Damage Disorders or the Treatise on Cold Injury)," established by one of the most famous ancient Chinese physicians, Zhang Zhongjing (150–219 AD). SNS has shown significant inhibition on tumor growth in HepG2 xenograft model. Lin et al. elucidated the molecular mechanism by which SNS exerted an antimigratory and anti-invasive effect on HBx-activated liver cancer cells. These results showed that SNS suppressed invasiveness and metastasis in HCC cells via multiple signal transduction pathways including downregulating PI3K/Akt, decreasing MAPK and IκB signaling, inhibiting NF-κB and AP-1 activity, and reducing MMP-9 expression. Thus, SNS might be helpful to interfere the invasion and metastasis of HCC [75].

Songyou Yin (SYY), a composite formula, showed efficacy to repress tumor proliferation, metastasis, and recurrence. An interesting study explored that SYY combining with moderate swimming has potent effect on retraining tumor growth and metastasis mainly via enhancing immune function [76].

Niu-Huang-Shen (NHS) has been accepted and used in China for a long time with its various effects such as antipyretic, anti-inflammatory, and vasodilatation effects. It was showed that NHS inhibited cell cycle arrest, induced cell apoptosis, and then repressed cell proliferation and invasion, probably through the significant suppression of Yes-associated protein (YAP) expression. NHS may have the therapeutic potential for treating HCC more effectively [77].

Shuihonghuazi formula (SHHZF) has been employed for early stage of liver cancer in clinical therapy for a long time; a study was designed to investigate potent effects of SHHZF on hepatoma and its metabolomic profiles. The results elucidated that SHHZF exerted inhibitory effects against liver cancer by adjusting the activities of PE N-methyl transferase, lysophospholipase D, methylenetetrahydrofolate reductase, and lysophospholipase [78].

3. Chinese medicine as a complementary treatment of liver cancer

Chinese medicine is appreciated for its 5000-year-old history and still holds a prominent position in primary health care in China. Chinese medicine could complement Western medicine by using modern techniques; thus, increasing interests in Chinese medicine has been observed over the Western world. In Chinese medicine, a wide range of ingredients have been proven to achieve various effects in cancer therapy, including alleviating the toxicity to human body, retraining tumor metastasis and recurrence, enhancing chemo- or radio-therapeutic effects, and subsequent improving the general status of patients and extending their survival time.

Long-term food restriction and diarrhea may be an adverse factor for liver cancer. Jian-pi-jie-du decoction (JPJD) could improve the quality of life of hepatoma subjects, in particular, the symptoms of diarrhea and decreased food intake. A research indicated JPJD could improve the condition of tumor-bearing rats, which were pretreated with diarrhea and food restriction by increasing ABCC2 expressional level and downregulating the OATP1B2 in liver normal tissues while downregulating ABCC2 as well as upregulating OATP1B2 in cancer tissues [79].

In terms of radioprotective and radiosensitizing functions of Chinese medicine, a series of concerning studies have been conducted. Numerous Chinese medicine agents have been confirmed to strengthen the therapeutic gain of radiotherapy by the way of serving as radioprotectors for healthy cells or as radiosensitizers for cancer cells [80, 81]. Botanical agents are comprised of multiple phytochemical compounds that may work synergistically or even individually, not only exhibiting favorable therapeutic effects, but also with safety profiles and lower toxicity [82].

Ganoderma lucidum polysaccharide (GLP) is well known for its various pharmacologic properties including antitumor effects [52]. A study recently demonstrated that GLP treatment may augment growth inhibition and apoptotic death of HepG2 cells, which induced by radiation, and revealed the regulatory role of Akt signaling pathway for GLP-mediated radiosensitivity in HCC cells exposed to radiation [83].

Kou et al. investigated the radiosensitizing effects of ultrafiltration extract of Radix Angelicae Sinensis-Radix Hedysari (RAS-RH) in human hepatoma cells. The results reported that the RAS-RH significantly enhanced the radiosensitivity of H22 cells of 12C6+ heavy ion radiation. Further study explored the underlying mechanism of radiosensitization, which is to increase caspase-dependent apoptosis via reducing surviving expressional level, suggesting a promising potent radiosensitizer [84].

Zhang et al. demonstrated that a flavonoid dihydromyricetin (DHM) exerted anticancer activity against hepatoma cells as well as xenotransplanted tumors in nude mice by activating the p53-dependent apoptosis pathway. And best of all, DHM was indicated to play a prominent role when administered in combination with cisplatin [85]. In this case, DHM could be an ideal anticancer drug with minimal side effects because it can alleviate cytotoxicity caused by cisplatin in normal liver cells.

Some studies investigated the adjunctive role of bufalin in reversal chemoresistance in the treatment of liver cancer. The Akt activation triggered by sorafenib is regarded to be responsible for this resistant phenomenon. Zhai et al. investigated that bufalin had the ability of reversing both inherent and acquired resistance to sorafenib via the IRE1 pathway in an ER-stress-dependent manner. These data warranted further studies to examine the utility of bufalin in combination with sorafenib as a first- or second-line treatment after sorafenib alone gains failure in advanced liver cancer [86]. Fluorouracil (5-FU) is a type of anticancer chemotherapeutics, which has been used for 40 years in clinical practice. A research confirmed the reversal effect of bufalin on drug resistance in a moderate multidrug resistance cell line Bel-7402/5-FU. They found Bufalin could block the cell cycle at G_0/G_1 phase, induce apoptosis through an increase of Bax/Bcl-xL ratio, inhibit the drug efflux pump activity via downregulation of MRP1, and reduce the expression of thymidylate synthase in vitro. All these data revealed that in Bel-7402/5-FU cells, the combination of bufalin with cytotoxic drugs could considerably reverse the MDR through multiple pathways including cell cycle arrest, apoptosis induction, etc., indicating an effective strategy for the chemotherapy of HCC [87].

Xu et al. investigated the efficacy of drug combination of luteolin and 5-FU on the proliferation of HepG2 and Bel-7402 cells. The data showed that luteolin synergized 5-FU at different dose ratios and then exerted the antitumor effects against HCC cells. Potential mechanism for

synergistic effects may be associated with apoptosis and 5-FU metabolism, as evidenced by the increased bax/bcl-2 ratios, upregulated p53 expressions, and induced PARP cleavage [88].

ADCX, a natural cycloartane triterpenoid isolated from *Cimicifugae* rhizome, impaired autophagic degradation by inhibiting lysosomal cathepsin B expression in multidrug resistant cell line, namely HepG2/ADM, which consequently lead to apoptosis, suggesting that an active constituent from Cimicifugae rhizome could overcome multidrug resistance in hepatoma cells by the role of persistent Akt activation in inhibition of autophagic degradation [89].

Arsenic trioxide (As_2O_3) with high doses is employed to treat solid tumors and acute promyelocytic leukemia, which mostly induce toxic side effects to healthy cells. Andrographolide is a kind of Chinese medicine that exhibits various effects against diseases such as anti-inflammatory, antivirus, antitumor, and so on. Duan et al. demonstrated that andrographolide enhanced As_2O_3-induced apoptosis in a caspase-3-dependent manner via downregulation of EphB4 in HCC cells. These findings suggested that lower concentrations of As_2O_3 in combination with andrographolide could be used as chemotherapy for HCC with the potential to minimize the adverse events from As_2O_3 treatment alone [90].

The aqueous extract of *Solanum nigrum* (AE-SN) is an important constituent in some Chinese medicine formulae used in the treatment of cancer. Wang et al. explored the antitumor effect of AE-SN in combination with a normal chemotherapeutic drug, namely doxorubicin or cisplatin, in HCC cell lines Hep3B and HepJ5. The results indicated the integrated treatment with AE-SN-potentiated doxorubicin and cisplatin-induced cytotoxicity through the cleavage of caspase-7 and accumulation of microtubule-associated protein-1 light chain-3 A/1B II (LC-3 A/B II), which were involved in autophagic and apoptotic cell death, respectively. Thereby, this combinatorial strategy of AE-SN and cisplatin or doxorubicin may be exploited to be a candidate regimen to treat HCC patients [91].

A recent research was performed to explore the combination effect of Huaier aqueous extract and chemotherapeutic agent cisplatin or rapamycin. The findings showed that Huaier had the capacity of activating mTOR signaling, which contributed to the enhanced cancer cells sensitivity to chemotherapeutics in response to Huaier administration. Huaier, thus, can potentially be used in integrated chemotherapy with rapamycin or cisplatin for liver cancer therapy [92].

Cinobufacini, a mixture of a number of components in Chinese medicine, has been used extensively for HCC therapy with strong apoptosis-inducing activity. Xia et al. used a combination of doxorubicin with cinobufacini to achieve tumor-suppression efficiency and found the combination group had a more considerable apoptotic effect by affecting proteins and RNA of apoptosis-related elements, such as Bcl-2, Bax, Bid, and cytochrome C. Consequently, cinobufacini in combination with chemotherapeutic agents might be a new strategy to improve the treatment effect for HCC patients [93].

Shufeng Jiedu Capsule (SFJDC) has been widely used due to its various pharmacological actions such as anti-inflammation, antibacterial, antiviral, and antitumor. Recently, scholars used combination of SFJDC with doxorubicin to treat liver cancer cells and further explored the underlying mechanisms of SFJDC as well as its constituents in vitro. The data showed that the combination group induced more considerable apoptosis and invasion and migration suppression than control group by targeting NF-κB, Akt/mTOR, and mitochondrial signaling pathways [94].

Dahuang zhechong pill (DHZCP) is one of the most famous prescriptions from an ancient Chinese medical classic "Jin Kui Yao Lue (Essential Prescriptions from the Golden Cabinet)." DHZCP is officially recorded in the Chinese Pharmacopeia and is commonly used for clinical practice of hepatoma. Wu et al. found that inhibitory growth of doxorubicin-resistant HCC subcutaneous xenografts in nude mice was achieved by DHZCP, and apoptosis promotion was accelerated by doxorubicin. The reversal of doxorubicin resistance by DHZCP was related with energy metabolism decline and regulation of proapoptotic proteins expression [95].

4. Discussion

Accumulating researches have demonstrated that Chinese medicine is a promising substitute for therapy of liver cancer. Furthermore, increasing scholars starts to pay attention to clinical studies of Chinese medicine. For example, gambogic acid (GA), a naturally occurring compound from ancient China, has been demonstrated efficient antineoplastic activity in a number of malignancies. More importantly, it has entered phase II clinical trials. A team ?found GA might lead to oxidative stress and subsequently induce apoptosis in hepatoma cells through interacting with TrxR1. Thus, targeting TrxR1 by GA disclosed a previously unrecognized mechanism underlying the biological action of GA and provides useful information for further development of GA as a potential agent for cancer therapy [96]. On the other hand, the theory of "Jianpi Huayu Therapy" (JPHY) was rooted from "Jin Kui Yao Lue." According to the selection criteria, Zhong et al. recruited a total of 120 patients in a randomized trial, aiming to compare the curative outcome and safety profile of surgery in combination with "Jianpi Huayu Therapy" HCC treatment to surgery alone. The patients in treatment group received the basic prescription based on JPHY. The results showed that hepatectomy combined with JPHY was more effective with reducing postoperative metastasis and recurrence and prolonged overall survival of HCC patients [97]. JQ1, one of the bromodomain and extra-terminal domain (BET) inhibitors, has been emerged as a novel agent candidate for cancer treatment in clinical research. Nevertheless, a number of solid cancers are resistant to BET inhibitors. The results from a group showed that oridonin synergistically increased JQ1 capacity of inhibiting HCC cell survival, and considerably enhanced JQ1-caused apoptosis in HCC cells and in HCC cancer stem-like cells. Furthermore, they demonstrated that oridonin distinctly augmented the sensitivity of JQ1 via downregulation of the level of multiple antiapoptotic proteins, including Bcl-2, Mcl-1, and x-linked inhibitor of apoptosis, suggesting that the combination treatment of JQ1 and oridonin could be further pursued for clinical application and it was expected to provide a rational for HCC tumor prevention [98].

Collectively, the aforementioned findings showed the potential efficacy of Chinese medicine on numerous types of cancer, either alone or in combination with conventional treatment of method such as surgery, chemotherapy, or radiation. In particular, as stated above, when integrated with chemotherapy or radiotherapy, Chinese medicine may serve as complementary drugs strongly enhancing the positive effects or reducing the negative events induced by radiochemotherapy. However, in comparison with a great deal of laboratory researches, clinical trials still remain poor, which limits the wide application of Chinese medicine throughout the world.

5. Conclusion

Chinese medicine is increasingly emerging as a novel curative choice for liver cancer. This retrospective review systemically introduced and evaluated the functional roles of Chinese medicine in treating liver cancer. Chinese medicine has potentially exerted efficient anticancer properties. For example, liver cancer progression can be repressed by active constituents derived from Chinese medicine through multiple pathways. The specific network with regard to the potential therapeutic targets for liver cancer treatment was constructed (**Figure 1**). The detailed relationships between biological factors and refined extracts could be directly visualized in **Figure 1**. Moreover, composite formulae as promising curative are increasingly indispensable in current clinical practice. As summarized in **Table 1**, formulae potentially employed in practice were studied in laboratory and the regulatory mechanisms for the treatment of liver cancer have been showed clearly. Also, Chinese medicine may serve as adjuvant agents in surgery as well as in combination with conventional radio- and chemotherapy, to decrease the adverse events or enhance the treatment outcome. Taken all together, Chinese medicine possesses the potential in liver cancer treatment, and rational application in clinical therapy needs to be warranted in the future.

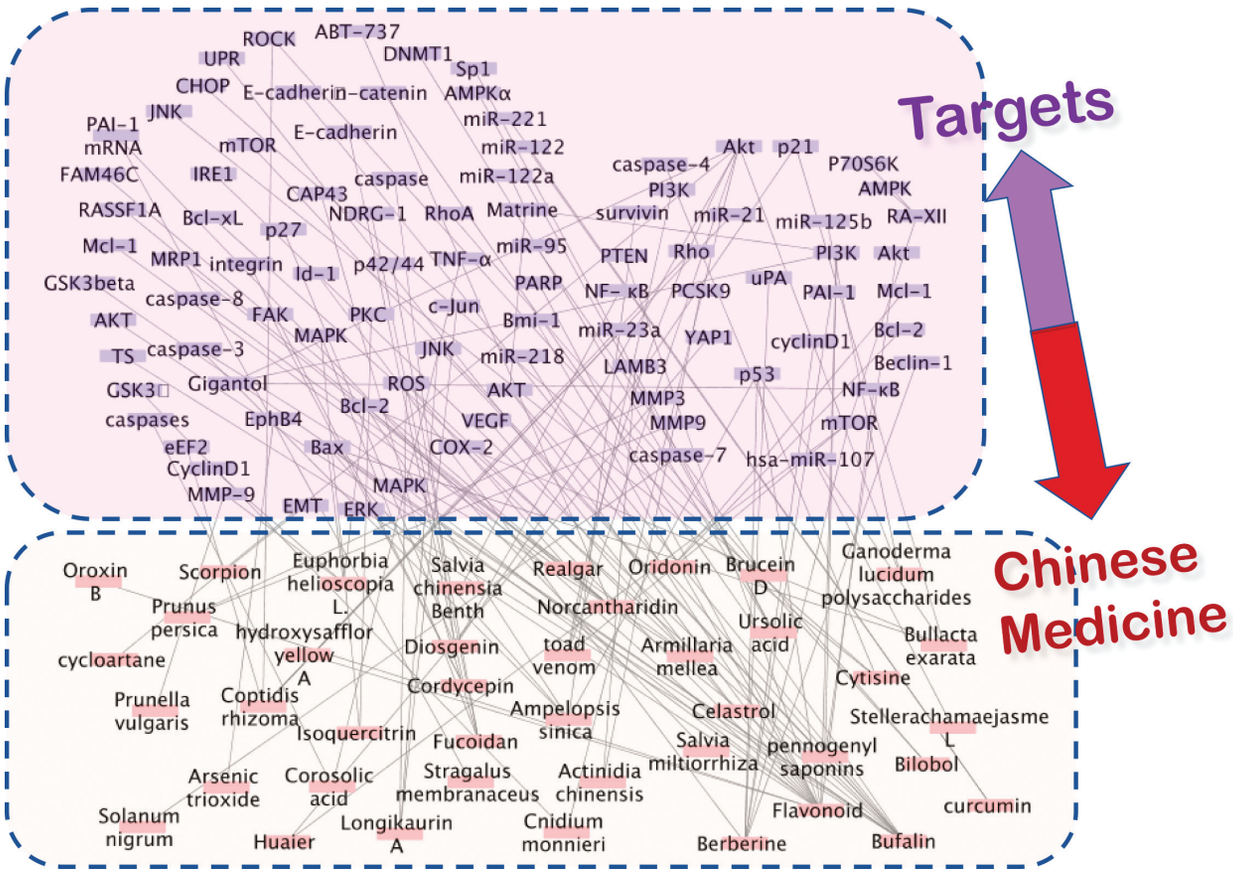

Figure 1. Target identification of Chinese medicine-derived compounds and extracts for liver cancer. Literature mining in PubMed with "Chinese Medicine" integrated with "liver cancer" was performed. All filtered data during the last 5 years were imported into a professional software Cytoscape for the establishment of the analysis of network pharmacology. The top five influential molecules including Akt, Bax, Bcl-2, mTOR, and PI3K could be figured out.

Name	Functions	Ref.
Huang-lian-jie-du-tang	Cell cycle arrest, induce mitochondrial apoptotic pathway, inhibit HCC cell proliferation, suppress growth and angiogenesis in xenografted murine model	[71, 72]
Yiguanjian	Interfere proliferation suspension and induce anoikis in cancer cells	[73]
Pien Tze Huang	Inhibit cancer cell proliferation and induce apoptosis	[74]
Sini-San	Suppressed invasiveness and metastasis in HCC cells	[75]
Songyou Yin	Repress tumor proliferation, metastasis, and recurrence	[76]
Niu-Huang-Shen	Cell cycle arrest, induce cell apoptosis, and cell invasion	[77]
Shuihonghuazi formula	Increase the uptake and utilization of linoleic acid and oleic acid, increase arachidonic acid-like substance content, and enhance organism immunity of liver cancer rats	[78]
Jian-pi-jie-du decoction	Improve the condition of tumor-bearing rats with the symptoms of diarrhea and decreased food intake	[79]
Cinobufacini	Combination of doxorubicin with cinobufacini to achieve a more considerable apoptotic effect	[93]
Shufeng Jiedu Capsule	Combination of SFJDC with doxorubicin induced more considerable apoptosis and invasion and migration suppression	[94]
Dahuang zhechong pill	Inhibit growth of doxorubicin-resistant HCC subcutaneous xenografts in nude mice and accelerate apoptosis promotion integration with doxorubicin	[95]

A comprehensive screening among literature searched with "Chinese Medicine" combined with "liver cancer" was performed. Potential composite formulae for therapeutic of liver cancer were screened out and corresponding possible action mechanisms were summarized.

Table 1. Summary on Chinese medicine composite formulae potentially used for liver cancer treatment.

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