

REVIEW ARTICLE

Traditional Chinese medicine as supportive care for the management of liver cancer: Past, present, and future

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Received 27 September 2019; received in revised form 23 October 2019; accepted 25 October 2019
Available online 2 November 2019

KEYWORDS

Chinese herbal medicine;
Hepatocellular carcinoma;
Molecular mechanism;
Network pharmacology;
Traditional Chinese medicine

Abstract Liver cancer is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer death worldwide. Western medicine and therapies are the primary treatment strategies of hepatocellular carcinoma (HCC), but the general prognosis for HCC patients is still dismal. Under these circumstances, HCC prevention is particularly important. Traditional Chinese medicine (TCM) encompasses a wealth of documented therapeutic resources, and “preventative treatment” is the principle of TCM. In China, TCM has been used for HCC prevention for thousands of years, and has also been demonstrated to be effective for the treatment of HCC in modern China. However, the TCM theory for prevention and treatment of HCC is more widely accepted in China than abroad. In this review, we first summarize the herbs and ancient formulas with therapeutic effects on HCC. We also review the research status of TCM in modern medicine as well as the current obstacles in its development. Finally, we discuss the future of TCM in the context of precision and integrated medicine. After reviewing the literature, we believe that TCM, through ancient development, is an advanced method of cancer treatment with positive curative effects, despite its surrounding controversy. Furthermore, precise analyses and systematic research methods provides novel approaches to modernize TCM for the future.

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Peer review under responsibility of Chongqing Medical University.

Introduction

Liver cancer is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer deaths worldwide.¹ Hepatocellular carcinoma (HCC) is the major histological subtype of primary liver cancers, accounting for 80% of the total liver cancer burden in the world. In China, HCC represents 50% of the diagnosed cases and deaths.² HCC is associated with several risk factors—hepatitis viral infection, environmental toxins, oxidative stress, chronic inflammation, hepatotoxic drugs—and is involved in the development of chronic inflammation, fibrosis, and carcinogenesis.^{3,4} Western medicine and therapies are the primary strategies for the treatment of HCC (e.g., surgical resection, liver transplantation, radiofrequency, chemotherapy, and targeted molecular therapy), but the general prognosis for HCC patients is still dismal.⁵ With roots in ancient China, traditional Chinese medicine (TCM) has been used for the treatment of cancers, including HCC. TCM is based on empirically accumulated knowledge and has achieved curative effects.⁶ In modern China, TCM is the most widely used form of complementary and alternative medicine that benefits HCC patients, either alone or in combination therapies.^{6–9}

TCM encompasses a wealth of documented therapeutic resources, with two main parts: the TCM theoretical system and Chinese herbal medicine (CHM). “Preventative treatment” is the principle of TCM for controlling disease, which was recorded in *Huang-di-nei-jing*, the authoritative book of TCM written over 2000 years ago. Etiology is central to TCM theory which studies the *zheng* (syndromes) of cancers based on holism (the whole condition). In TCM theory, cancers are related to the disequilibrium of *yin* and *yang* and deficiency of vital *qi* (energy). Holism holds that the liver is the soul of the human body, which stores the blood, controls the sinews, and maintains a smooth and uninterrupted flow of *qi*.¹⁰ The causes of HCC are *yu* (stasis), *du* (toxicity) and *xu* (deficiency). Strategies of treatments include *huo-xue-hua-yu* (removing blood stasis), *jian-pi-li-qi* (regulating the flow of *qi* and strengthening the spleen), or *qing-re-jie-du* (clearing heat and detoxifying).¹¹

The system of TCM came into being in the Spring and Autumn period and reached its peak in the Song, Yuan, and Ming dynasties (Fig. 1). Although TCM has been questioned throughout history and even neglected in modern times, it still plays an important role in the treatment of chronic diseases, especially for tumor therapy. Chinese practitioners of TCM focus on the inherent balance of body,¹² therefore, TCM works not just by directly inhibiting cancer itself, but also by playing an indirect role by treating the patient as a whole.^{13,14} For HCC, many effective *fang-ji* (formulas) have been clinically proven to retard HCC progression and prevent HCC occurrence.^{10,15–20} The *fang-ji* were designed on the TCM theory of disequilibrium of *yin* and *yang* and *qi* and *xue*.

In this review, we first summarize the herbs and ancient formulas with therapeutic effects on HCC. Then, we review the research status of TCM in modern medicine and raise existing problems in the development of TCM. Finally, we speculate about the future of TCM in the context of precision medicine and integrated medicine. After reviewing

the literature, we believe that TCM, though developed in ancient times, is an advanced method of cancer treatment that, although not without some controversy, has positive curative effects. Precise analysis and systematic research methods are still needed to verify the TCM theory.

History of TCM for HCC prevention and therapy

Classical herbal formulas, which were used for preventing and treating hepatic diseases thousands of years ago, are the most common application of TCM. Herbs were classified by function: toning *qi*, invigorating blood, nourishing *yin*, soothing liver *qi* stagnation, clearing heat, detoxifying, and dissolving stasis, all of which were potential sources for prevention and treatment of HCC. Although CHM has been demonstrated and documented to be effective for the treatment of HCC,^{21–23} critics point out that the toxicity of CHM is unclear.²⁴ Also, the TCM theory for prevention and treatment is more widely accepted in China than abroad. Modern medicine requires a clear understanding of the effector compounds, toxic ingredients, and the associated signaling pathways of CHM. After years of research, great progress has been discerning the active compounds and associated signaling pathways in CHM,²⁵ but the active compounds are not a substitute for the complete CHM formula. TCM therapy treats HCC holistically, but the actual anticancer mechanism of the CHM formula is still unknown. In recent years, systems pharmacology, in particular, the subfield of network pharmacology, has emerged as a promising approach to elucidate the CHM’s mechanisms of action and promote methodical drug discovery, thus facilitating the modernization of TCM.^{26,27}

Curative effects drove development of TCM for HCC in ancient times

Herbs for prevention and therapy of HCC

TCM covers thousands of species of plants, and for HCC therapy, many of these herbs are commonly used. The ten most commonly used herbs [Fuling (*Poria*), Huangqi (*Astragali Radix*), Baihuasheshecao (*Hedyotidis Herba*), Baizhu (*Atractylodis Macrocephalae Rhizoma*), Gancao (*Glycyrrhizae Radix et Rhizoma*), Baishao (*Paeoniae Radix Alba*), Chaihu (*Bupleuri Radix*), Danggui (*Angelicae Sinensis Radix*), Dangshen (*Codonopsis Radix*), and Biejia (*Trionycis Carapax*)] affect *huo-xue-hua-yu*, *jian-pi-li-qi*, and *qing-re-jie-du*. Additional herbs have been used for HCC therapy since ancient times, as detailed in Table 1.

Formulas for prevention and therapy of HCC

Formulas are the most common application of CHM, and some classical herbal formulas have remarkable prevention and treatment effects on HCC. *Ren-shen-bie-jia-jian* and *xiao-chai-hu-tang* are formulas used for inhibiting hepatocarcinogenesis through nourishing *qi* and soothing liver *qi* stagnation. In the TCM theory, the liver and kidney share the same origin, so the formulas of *zi-yin-tang* and *fu-zheng-hua-yu-tang* were used for prevention of HCC by toning the liver and kidney. Strengthening the spleen is another important principle for HCC therapy, and *jian-pi-*

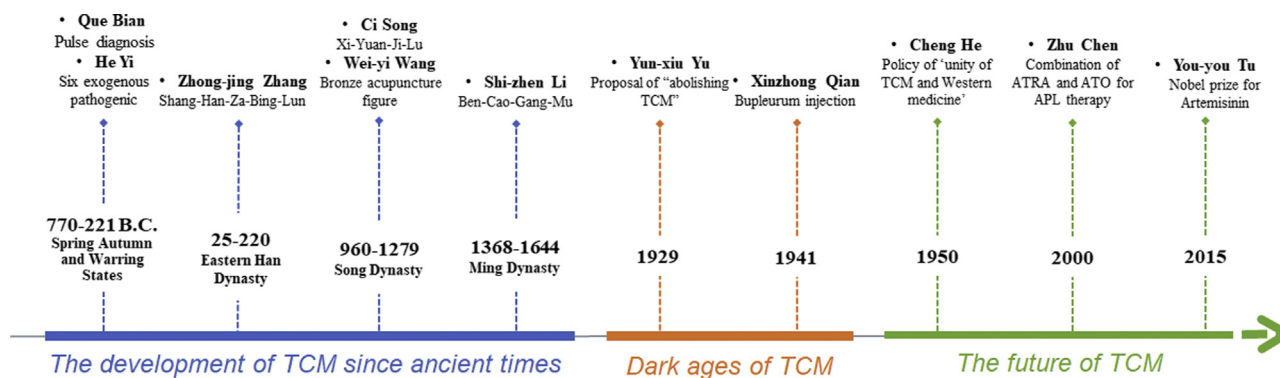


Figure 1 Development of traditional Chinese medicine. TCM started in the Spring and Autumn period, reaching its peak in the Song, Ming, and Qing dynasties. Although TCM has been questioned continuously throughout its history and even discounted in modern times, it still plays an important role in the treatment of chronic diseases, especially in the field of tumor therapy. In 1950, the idea of unifying TCM and Western medicine was proposed, and TCM has been gaining in popularity ever since. In 2015, Tu Youyou won the first Nobel Prize in Physiology or Medicine, a high-profile breakthrough for TCM, and attracted the world's recognition of TCM again. Abbreviations: ATRA: All-trans retinoic acid; ATO: Arsenic trioxide; APL: Acute promyelocytic leukemia.

jie-du recipe was a famous herbal formula for strengthening the spleen and for detoxification. In addition to toning treatments, directly eliminating pathogenic factors is another principle of HCC using formulas such as *qing-re-jie-du-tang* and *zao-lian* mixture. Danshen and Jianghuang are anti-HCC herbs effective at inhibiting HCC by dissolving stasis. Additional formulas have been validated since ancient times, and details are described in Table 2.

The shortcomings of TCM theory and CHM

TCM practice relies on a combination of TCM theory and the personal experience of physicians, without standardized protocols for anti-HCC treatment. TCM theory is not widely accepted, which is a major obstacle for modernizing TCM. Molecular and cell biology in contemporary medicine have provided important insights into the pathogenesis of HCC and offer anti-HCC strategies. In addition, some toxic ingredients of CHM were reported, which further hindered the development of TCM. Therefore, exploration of the molecular signaling mechanisms of CHM as well as removal of toxic ingredients may provide support for the modern acceptance of TCM.²⁸

Application and research status of TCM for HCC patients in modern medicine

Status of CHM in HCC patients

CHM for HCC prevention. The cure rate of HCC is unsatisfactory, so prevention is particularly important.²⁹ In China, TCM has long been used for HCC prevention and are viewed as effective preventative treatments. One clinical trial showed that the herb-derived compound oxymatrine had a hepatitis B virus-suppressing effect in 216 chronic hepatitis B patients.³⁰ Glycyrrhizin and silymarin (also herb-derived compounds) have been demonstrated to reduce the incidence of HCC in patients with chronic hepatitis C virus infection and fibrosis.^{31,32} The classic formulas such as *jian-pi-huo-xue* and *xiao-chai-hu-tang* are also effective at inhibiting hepatocarcinogenesis in patients with hepatitis (B and C viruses) and cirrhosis.^{33,34}

CHM for anti-HCC therapy. Based on TCM theory, the clinical use of CHM is commonly prescribed as an herbal

Table 1 Types of herbal treatments for HCC patients.

TCM therapeutic principles	Herbs
Supplementing <i>qi</i>	Baizhu (<i>Atractylodis Macrocephalae Rhizoma</i>), Huangqi (<i>Astragali Radix</i>), Dangshen (<i>Codonopsis Radix</i>), Danggui (<i>Angelicae Sinensis Radix</i>), Shanyao (<i>Dioscoreae Rhizoma</i>), Gancao (<i>Glycyrrhizae Radix et Rhizoma</i>), Baishao (<i>Paeoniae Radix Alba</i>), Biejia (<i>Trionycis Carapax</i>)
Clearing heat and detoxifying	Baihuasheshecao (<i>Hedyotidis Herba</i>), Banzhilian (<i>Scutellariae Barbatae Herba</i>), Shengdihuang (<i>Rehmanniae Radix</i>), Zhizi (<i>Gardeniae Fructus</i>), Huangqin (<i>Scutellariae Radix</i>), Qinghao (<i>Artemisiae Annuae Herba</i>)
Invigorating blood and dissolving stasis	Ezhu (<i>Curcumae Rhizoma</i>), Danshen (<i>Salviae Miltiorrhizae Radix et Rhizoma</i>), Yujin (<i>Curcumae Radix</i>), Tubiechong (<i>Eupolyphaga Steleophaga</i>)
Percolating dampness	Fuling (<i>Poria</i>), Yiyiren (<i>Coicis Semen</i>), Yinchen (<i>Artemisiae Capillaris Herba</i>), Cheqianzi (<i>Plantaginis Semen</i>), Yumixu (<i>Maydis Stigma</i>), Houpo (<i>Magnoliae Officinalis Cortex</i>), Dahuang (<i>Rhei Radix et Rhizoma</i>), Yuanhua (<i>Genkwa Flos</i>)
Rectifying <i>qi</i>	Zhiqiao (<i>Aurantii Fructus</i>), Chenpi (<i>Citri Reticulatae Pericarpium</i>)
Releasing the exterior	Chaihu (<i>Bupleuri Radix</i>), Guizhi (<i>Cinnamomi Ramulus</i>)

Table 2 Types of herbal formulas for treatment of HCC patients.

Herbal formulas	Ingredients	TCM therapeutic principles	Provenance
Shi-Quan-Da-Bu-Tang	Renshen (<i>Ginseng Radix et Rhizoma</i>), Baizhu (<i>Atractylodis Macrocephalae Rhizoma</i>), Fuling (<i>Poria</i>), Gancao (<i>Glycyrrhizae Radix et Rhizoma</i>), Chuanxiong (<i>Chuanxiong Rhizoma</i>), Danggui (<i>Angelicae Sinensis Radix</i>), Shudihuang (<i>Rehmanniae Radix Praeparata</i>), Baishao (<i>Paeoniae Radix Alba</i>), Huangqi (<i>Astragali Radix</i>), Rougui (<i>Cinnamomi Cortex</i>)	Toning <i>qi</i> and blood	Tai-ping-hui-min he-ji-ju-fang
Xue-Fu-Zhu-Yu-Tang	Chaihu (<i>Bupleuri Radix</i>), Gancao (<i>Glycyrrhizae Radix et Rhizoma</i>), Zhiqiao (<i>Aurantii Fructus</i>), Chuanxiong (<i>Chuanxiong Rhizoma</i>), Danggui (<i>Angelicae Sinensis Radix</i>), Shengdihuang (<i>Rehmanniae Radix</i>), Chishao (<i>Paeoniaeradix Rubra</i>), Taoren (<i>Persicae Semen</i>), Honghua (<i>Carthami Flos</i>), Niuxi (<i>Achyranthis bidentatae Radix</i>), Jiegeng (<i>Platycodonis Radix</i>)	Promoting blood circulation and dissolving stasis	Yi-lin-gai-cuo
Xiao-Chai-Hu-Tang	Chaihu (<i>Bupleuri Radix</i>), Huangqin (<i>Scutellariae Radix</i>), Shengjiang (<i>Zingiberis Rhizoma Recens</i>), Banxia (<i>Pinelliae Rhizoma</i>), Dazao (<i>Jujubae Fructus</i>), Dangshen (<i>Codonopsis Radix</i>), Gancao (<i>Glycyrrhizae Radix et Rhizoma</i>)	Soothing liver <i>qi</i> stagnation, and balancing <i>yin</i> and <i>yang</i>	Shang-han-lun
Chai-Hu-Shu-Gan-Tang	Chaihu (<i>Bupleuri Radix</i>), Chenpi (<i>Citri Reticulatae Pericarpium</i>), Zhiqiao (<i>Aurantii Fructus</i>), Xiangfu (<i>Cyperis Rhizoma</i>), Chuanxiong (<i>Chuanxiong Rhizoma</i>), Baishao (<i>Paeoniae Radix Alba</i>), Gancao (<i>Glycyrrhizae Radix et Rhizoma</i>)	Soothing liver <i>qi</i> , balancing blood, and relieving pain	Jing-yue-quan-shu
Qing-Hao-Bie-Jia-Tang	Qinghao (<i>Artemisiae Annuae Herba</i>), Biejia (<i>Trionycis Carapax</i>), Xishengdi (<i>Rehmanniae Radix</i>), Zhimu (<i>Anemarrhenae Rhizoma</i>), Mudanpi (<i>Moutan Cortex</i>).	Nourishing <i>yin</i> and refreshing liver	Wen-bing-tiao-bian
Jia-Wei-Si-Jun-Zi-Tang	Renshen (<i>Ginseng Radix et Rhizoma</i>), Baizhu (<i>Atractylodis Macrocephalae Rhizoma</i>), Huangqi (<i>Astragali Radix</i>), Fuling (<i>Poria</i>), Gancao (<i>Glycyrrhizae Radix et Rhizoma</i>), Baibiandou (<i>Lablab Semen Album</i>)	Toning spleen, nourishing <i>qi</i> , soothing liver <i>qi</i> , and dissolving stasis	San-yin-ji-bian-zhen-fang-lun
Bu-Zhong-Yi-Qi-Tang	Huangqi (<i>Astragali Radix</i>), Renshen (<i>Ginseng Radix et Rhizoma</i>), Danggui (<i>Angelicae Sinensis Radix</i>), Shengma (<i>Cimicifugae Rhizoma</i>), Gancao (<i>Glycyrrhizae Radix et Rhizoma</i>), Chenpi (<i>Citri Reticulatae Pericarpium</i>), Chaihu (<i>Bupleuri Radix</i>), Shengjiang (<i>Zingiberis Rhizoma Recens</i>), Dazao (<i>Jujubae Fructus</i>), Baizhu (<i>Atractylodis Macrocephalae Rhizoma</i>)	Invigorating spleen and stomach and toning <i>qi</i>	Pi-wei lun
Yi-Guan-Jian	Beishashen (<i>Glehniae Radix</i>), Maidong (<i>Ophiopogonis Radix</i>), Danggui (<i>Angelicae Sinensis Radix</i>), Gouqi (<i>Lycii Fructus</i>), Shengdihuang (<i>Rehmanniae Radix</i>), Chuanlianzi (<i>Toosendan Fructus</i>)	Toning kidneys, nourishing <i>qi</i> and <i>yin</i> , and draining dampness	Xu ming-yi-lei-an
Huang-Lian-Jie-Du-Tang	Huanglian (<i>Coptidis Rhizoma</i>), Huangqin (<i>Scutellariae Radix</i>), Huangbo (<i>Phellodendri chinensis Cortex</i>), Zhizi (<i>Gardeniae Fructus</i>)	Clearing heat, Detoxification, and draining dampness	Wai-tai-mi-yao
Long-Dan-Xie-Gan-Tang	Longdancao (<i>Gentianae Herba</i>), Zhizi (<i>Gardeniae Fructus</i>), Gancao (<i>Glycyrrhizae Radix et Rhizoma</i>), Danggui (<i>Angelicae Sinensis Radix</i>), Shengdihuang (<i>Rehmanniae Radix</i>), Huangqin (<i>Scutellariae Radix</i>), Mutong (<i>Akebiae Caulis</i>), Zexie (<i>Alismatis Rhizoma</i>), Cheqianzi (<i>Plantaginis Semen</i>), Chaihu (<i>Bupleuri Radix</i>)	Clearing heat, detoxification, and draining dampness	Tai-ping-hui-min he-ji-ju-fang

formula, and Liao et al.³⁵ reported 19.50% outpatients with HCC received TCM services in Taiwan. For HCC patients in advanced stages ineffectively treated by Western medicine, *xiao-ai-ping* or *hua-chan-su* were always used as a monotherapy, and some patients had prolonged, stable disease or tumor shrinkage.^{36,37} Combination therapy is more common in clinical practice for HCC patients. The regimen of *jian-pi-jie-du* granules combined with *hua-chan-su* injection was associated with diminished risk when compared with transarterial chemoembolization (TACE) therapy in a small group of HCC patients.^{38,39} A combination of *ai-di*,^{40,41} *hua-chan-su*,^{42,43} and *xiao-ai-ping* injection⁴⁴ improved efficacy and reduced adverse reactions after TACE therapy for advanced-stage HCC patients.

CHM for improving symptoms of HCC patients. TCM is often considered as alternative therapy once HCC patients cannot benefit from radical therapy.⁷ Jinei jin and Maiya were the most commonly used herbs for treating anorexia; Dangshen and Huangqi for fatigue; Zhuru and Banxia for nausea and vomiting.⁴⁵ Cancer pain is also a common complication of advanced-stage HCC. Chanwu powder and modified Jinhuang powder can be externally applied to alleviate cancer-induced pain. Also, topical application of Chanwu powder avoids some side effects and reduces the patient's dependence on analgesics.⁴⁶

Research status of anti-HCC mechanisms of TCM

Diverse herbal formulas are commonly described in TCM theory. Herbs have many active components that make them effective.⁴⁷ Many herbal formulas and their active ingredients are effective at inhibiting cell proliferation and inducing cell senescence, inducing apoptosis and autophagy,

inhibiting metastasis and angiogenesis, improving drug resistance, and regulating immune function⁴⁸ (Fig. 2).

Inhibition of cell proliferation and induction of cell senescence. HCC is characterized by uncontrolled cell proliferation.⁴⁹ Formulas such as *son-you-yin*¹² and *so-cheong-ryong-tang*⁵⁰ as well as herbs including Danshen⁵¹ and Huangyaozi⁵² significantly inhibit cell proliferation and tumor growth in HCC. The compounds isolated from herbs Raddeanin A,⁵³ and Ardipusilloside-I⁵⁴ also showed anti-proliferative effects in HCC cells. Cell senescence induction is a novel approach for HCC treatment.⁵⁵ Ganoderiol F induces cell senescence by activating the extracellular-signal-regulated kinase (ERK) pathway and up-regulating the expression of p16.⁵⁶ *L. lucidum* Ait. fruit down-regulates retinoblastoma (RB) phosphorylation to induce cell senescence in HCC.⁵⁷

Induction of apoptosis and autophagy. Apoptosis is one of the most thoroughly studied cell processes in HCC.^{58,59} Many herbal compounds are effective at inducing apoptosis in HCC including Gypenoside, Isorhamnetin, Liquiritigenin, and N-Butylidenephthalide.^{60–63} Anoikis is another apoptotic process that occurs when a cell detaches from the extracellular matrix.^{64,65} Arecoline, Cuspidatum, Emodin, Polydatin, and Phycion induce anoikis through various related signaling pathways.^{66,67} Autophagy is a process that promotes cell death and is recognized as a target for HCC therapy because autophagy can contribute to anticancer therapeutic responses.^{68,69} Tetrandrine and Shikonin promote reactive oxygen species (ROS) generation and activate the ERK signaling pathway to induce autophagy in HCC cells.^{70,71} Conversely, Epigallocatechin-3-O-gallate strengthens

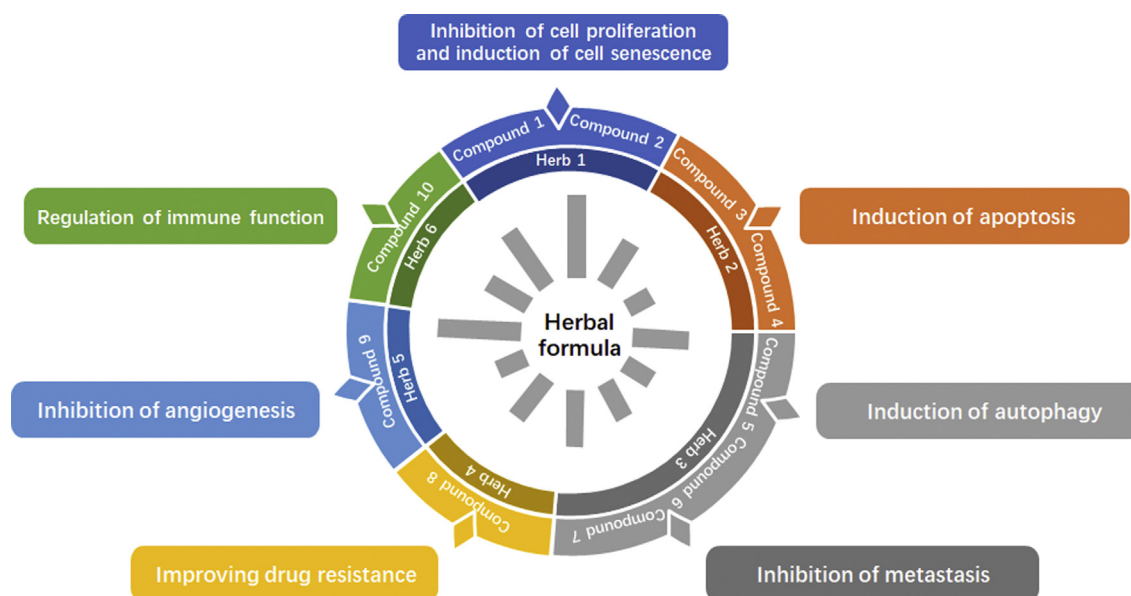


Figure 2 CHM herbal formulas contain multiple components to for holistic treatment. Herbal formulas are composed of many active components that make up the fundamental units of herbal action, such as the diverse mechanisms of anti-HCC formulas.

doxorubicin (DOX)-mediated anticancer effects in HCC cells, acting as an autophagy inhibitor.⁷²

Inhibition of metastasis and angiogenesis. Chinese herbal compounds have demonstrated potency in inhibiting invasion and metastatic potential in HCC.¹² Artemisinin,⁷³ Tanshinone IIA,⁷⁴ and Resveratrol^{75,76} inhibit HCC metastasis through down-regulation of MMP2 and up-regulation of TIMP2 and E-cadherin. The combination of multiple herbal ingredients comprising astragalosides, Astragalus polysaccharide, and salvianolic acids inhibit TGF- β 1-mediated invasion in HCC cells.⁷⁷ Angiogenesis (the process of new blood vessels generating from existing vessels) plays a crucial role in tumor growth and metastasis and is a potential target for HCC therapy.^{78,79} Herbal formulas composed of cinobufotalin, Panax notoginseng saponins, ginsenosides Rg3, and lentinan inhibit angiogenesis as well as the expression of VEGF, EGFR, and MMP-2 in HCC.^{76,80} Gekko-sulfated glycopeptide decreases bFGF secretion and inhibits angiogenesis in HCC, acting through the heparin/heparan sulfate receptor.⁸¹

Improving drug resistance. Drug resistance is one of the characteristics of HCC contributing to the poor prognosis.⁸² Some herbal compounds have direct effects against drug resistance in HCC cells. *Astragalus membranaceus* polysaccharides enhance the anti-tumor effects of Adriamycin in HCC by up-regulating IL-2, IL-6, and TNF- α and down-regulating MDR1.⁸³ Astragaloside II, another component from *A. membranaceus*, is effective in enhancing the cytotoxicity of 5-fluorouracil (5-Fu) in HCC through the down-regulation of P-gp phosphorylation of ERK1/2 signaling.⁸⁴ Ursolic acid also induces apoptosis in doxorubicin-resistant human HCC cells.⁸⁵

Regulation of immune function. T-lymphocyte activation plays a pivotal role in HCC malignancy.^{86–88} Polysaccharides isolated from *A. annua* L increase CD4⁺ and CD8⁺ T cells, as well as IFN- γ and IL-4 secretion in HCC.⁸⁹ Gastrodin up-regulates NF- κ B, IL-2, and BCL-2 in CD4⁺ T cells and enhances cytotoxic activities of CD8⁺ T cells against HCC.⁹⁰ Regulatory T cells (Tregs) function as negative immune regulators, and *Astragalus* polysaccharides inhibit FOXP3 expression and the proliferation of Tregs.⁹¹

Shortcomings of TCM for HCC treatment

Safety of TCM for HCC patients. CHM represents a huge and noteworthy reservoir for novel drug discovery, but CHM safety evaluation is necessary. Oral CHM formulas have developed rapidly, and their variety has increased. Many clinical studies by Chinese and Western medical researchers have verified the efficacy and safety of oral Chinese-patented medicines for liver cancer.^{92–95} In addition, much attention has been paid to the clinical application of CHM injections.^{96,97} However, the safety of CHM is still questioned because of the uncertainty of the ingredients in CHM, and the presence of toxic ingredients in CHM has also been reported.⁹⁸ Aristolochic acid (AA), an abundant and possibly toxic compound in *Aristolochia* plants and various natural herbs, was widely implicated in HCC.^{98,99}

Some researchers believe long-term use of CHM remains risky, and CHM still needs extensive basic and clinical experiments to evaluate safety.^{100,101}

The efficacy of CHM in ant-HCC is still being questioned. Much progress of TCM has been made in the research of anti-HCC, and some clinical studies have encouraging results.^{102–106} However, some formulas worked well on HCC, but monotherapy or use of isolated ingredients weakened effects or had no impact entirely.¹⁰⁷ The composition of CHM is very complex, and many bioactive components of CHM only exhibit powerful anticancer effects in vitro, or the anticancer effect is weak or lost when purified from the formula. Additionally, lack of high-level clinical research evidence severely limits the development of CHM.¹⁰⁸

Molecular network integration to modernize TCM for HCC treatment

TCM formulas are composed of multiple herbs to achieve the highest efficacy with the fewest side effects for HCC prevention and treatment. Despite the widespread use of formulas in clinical practice of CHM, the combination principles based on the TCM theory were very challenging to discern. A variety of targeted molecular drugs have emerged in tumor therapy, but the limited efficacy shows that a single target is not enough to shift the outcome of HCC. Changing the focus of anti-tumor therapy from precision to integration should benefit patients, and we believe CHM has the inherent advantages for a multi-component strategy.¹⁰⁹

TCM is a complex, mixed system with multiple components and multiple targets, and identifying potential bioactive molecules and the underlying mechanisms of combinations are essential tasks for TCM. Network pharmacology has emerged as a promising approach to accelerate drug development and elucidate the mechanisms of action of CHM and understanding the complex interactions among biological systems, drugs, and complex diseases.^{110,111} Network pharmacology provides a novel approach to promote drug discovery in a precise manner and at the systems level, modernizing TCM for the future.^{112,113} With the aid of systems pharmacology, the “drug-to-gene-to-target-to-disease subtype” network will be established, and the *fang-ji* design principles guided by TCM theory will be illuminated.

Conclusions and prospects

There are many obstacles to developing TCM in the context of modern medicine. Owing to its complexity, the holistic concept, and the study of *zheng*, TCM theory is often questioned; the unknown quality of herbs is a drawback for TCM; precise analyses needed for pharmacodynamic and toxicological mechanisms hinders the modern acceptance of TCM; and synergistic, additive, or antagonistic effects of the ingredients in CHM remains unclear. TCM views the human body as a complex, dynamic system and focuses on the balance of the human body, both internally and with its

external environment. Only by solving the issues mentioned above can TCM truly go global. TCM is an important feature of traditional Chinese culture. Like Zhaoyou Tang, an academician of the Chinese Academy of Engineering, described, “only when Western medicine learns from China can we create a new strategy for tumor therapy.”

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgement

This research project was mainly supported by the National Natural Science Foundation of China (81502694). This research project was also partly supported by the Fundamental Research Funds for the Central Universities (1191329835), Postdoctoral Science Foundation of China (2015M570330), and Key Projects of Ningxia Natural Science Foundation (NZ15130).

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