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Review Article

Preventive and therapeutic role of traditional Chinese herbal medicine in hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma (HCC) is one of the most prevalent malignancies worldwide. The clinical management of HCC remains a substantial challenge. Although surgical resection of tumor tissues seems promising, a high recurrence and/or metastasis rate accounting for disease-related death has led to an urgent need for improved postsurgical preventive/therapeutic clinical intervention. Developing advanced target-therapy agents such as sorafenib appears to be the only effective clinical intervention for patients with HCC to date, but only limited trials have been conducted in this regard. Because of their enhanced preventive/therapeutic effects, traditional Chinese herbal medicine (CHM)-derived compounds are considered suitable agents for HCC treatment. The CHM-derived compounds also possess multilevel, multitarget, and coordinated intervention effects, making them ideal candidates for inhibition of tumor progression and HCC metastasis. This article reviews the anticancer activity of various CHMs with the hope of providing a better understanding of how to best use CHM for HCC treatment.

Keywords: anticancer therapy; chemoprevention; Chinese herbal medicine; hepatocellular carcinoma

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide and ranks as the second leading cause of cancer-related death in Taiwan. In a clinical setting, the current major curative therapies such as liver transplantation, surgical resection, and local ablation offer only limited options for HCC treatment.[1] More than 70% of patients with HCC, however, fail to meet the criteria for receiving "curative therapies" due to the presence of tumor extension or detection of underlying liver disease such as cirrhosis or both.[2] Moreover, despite these curative therapies, the recurrence rate of HCC remains high. To improve the therapeutic outcome, many adjuvant treatment methods such as transarterial chemoembolization (TACE), radiotherapy, immunotherapy, chemotherapy, and other systemic treatments have been used, with frequently dismal results.[3] Although the recently developed advanced target-therapy agents such as sorafenib (a vascular endothelial growth factor receptor and tyrosine kinase inhibitor) have been used in clinical settings to prolong survival in patients with advanced HCC, their therapeutic potential to date is limited due to their high cost and the significant side effects associated with their use.[4] Much effort has been put into identifying alternative therapies to increase the efficacy of

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anticancer drugs, to decrease toxicities or side effects, and to improve quality of life and survival of patients. Based on recent reports, traditional Chinese herbal medicine (CHM) seems to be emerging as an intriguing and viable choice because of its multilevel, multitarget, and coordinated intervention effects against HCC. The extensive application of phytochemical and molecular biological approaches in many CHM-derived compounds has shown great potential in developing anti-HCC natural products.[5] In this article, we comprehensively discuss the current state of understanding and the underlying pharmacological mechanisms of different CHMs that are used as a chemopreventive/chemotherapeutic agent for HCC treatment.

2. Molecular pathogenesis of HCC

HCC is a multifactorial disease caused by viral hepatitis infection, alcohol consumption, tobacco use, and exposure to aflatoxin and certain other chemical agents.[6] Numerous studies have shown that development of HCC is a multistep process.[7] The disease is initiated by mutation in various oncogenic genes. It has been found that hepatitis B virus-associated *HCC* genes are involved in various aspects of physiological regulation including protein synthesis [ribosomal protein S5 (*RPS5*)], cytoskeletal organization [keratin-8 (*KRT8*)], apoptosis [Fas-associated protein with death domain-like apoptosis regulator (*CFLAR*)], ion transportation (adenosine triphosphate synthase H^+ transporting mitochondrial Fo complex subunit B1; *ATP5F1*), signal transduction (mitogen-activated protein kinase kinase kinase 5 and insulin-like growth factor binding protein 2), and metastasis (matrix metallopeptidase-9 or MMP-9).[8] Other genes associated with cell structure [vimentin (*vim*) and beta-actin (*ACTB*)], glycolysis (glyceraldehyde 3-phosphate dehydrogenase), and cell adhesion (lymphocyte function-associated antigen 3; CD58) have also been shown to be enriched in hepatitis C virus-mediated HCC tissues compared with normal tissues.[9] Genetic mutations in these genes trigger HCC progression by activating certain oncogenic pathways such as the Raf–MEK–ERK pathway, phosphatidylinositol 3-kinase/Akt/mammalian target of rapamycin pathway, Wnt/β-catenin pathway, insulin-like growth factor pathway, hepatocyte growth factor/c-MET pathway, and growth factor-regulated angiogenic signaling.[8] In addition to the intrinsic genetic/signaling regulation, a growing body of evidence has also suggested that host–viral interactions, including immune response-induced hepatocyte necrosis and inflammation-mediated regeneration, might also contribute to hepatocarcinogenesis.[10] In brief, from a pathological point of view, the following two main mechanisms prevail during hepatocarcinogenesis: (1) cirrhosis associated with hepatic regeneration following tissue damage caused by hepatitis infection, toxins (e.g., alcohol or aflatoxin), or metabolic influences; and (2) mutations occurring in single or multiple oncogenes or tumor-suppressor genes. Although both mechanisms have been linked with modulations in the numbers of cellular signaling pathways, it remains a substantial challenge to clarify how these two pathogenic mechanisms act synergistically for HCC development.[8]

3. Anti-HCC effects of traditional CHM

In contrast to the trials undertaken and procedures performed to combat other highly prevalent cancers, such as lung, breast, and colorectal cancers, relatively fewer medical interventions and trials are available with regard to HCC. This has led to an urgent need to develop new, active, and well-tolerated treatments to improve survival in patients with advanced HCC and to increase enduring remission after curative treatment.[11] Although further work would be required to elucidate the detailed mechanisms behind CHM-mediated anticancer effects, evidence accumulated in the past several decades confirms the preventive and therapeutic effects of using CHM against HCC. In addition, the cellular and molecular basis of anti-HCC activity of different CHMs has also gradually been uncovered.

3.1. *Scutellaria baicalensis*

Baicalein, a flavonoid present in the herbal medicine *sho-saiko-to* (i.e., TJ-9; also known as *xiao-chai-hu-tang* in Chinese), is a widely used CHM for anti-inflammatory and anticancer therapies. Baicalein is reported to inhibit the activity of topoisomerase II and suppress the proliferation of HCC cell lines by G_2/M phase cell cycle arrest *in vitro*.[12] Moreover, treatment with *Scutellaria baicalensis* decreases the expression of p53, ETS1, Cdc25B, p63, epidermal growth factor receptor, ERK1/2, X-linked inhibitor of apoptosis protein, hypoxia-inducible factor 2α, and Cdc25C and upregulates the activity of cyclin E in a dose-dependent manner, suggesting that *S. baicalensis* exerts anti-HCC effects on broad cell-signaling networks, thereby leading to a collective inhibition of cell proliferation.[13] In addition, baicalein decreased MMP-2, MMP-9, and urokinase-type plasminogen activator expression as well as inhibiting the activity of the ERK signaling pathway, implying that baicalein could possibly regulate HCC invasion and metastasis.[14] The anti-HCC activity of baicalein was also described *in vivo* in a recent study in which mice treated with baicalein extract showed a significantly decreased growth of HepG2 xenografts compared with the control groups.[15]

3.2. *Berberine*

Coptis chinensis and its major constituent berberine are frequently used in treating diabetes mellitus, diarrhea, acute enteritis, dysentery, delirium due to high fever, leukemia, and otitis media. Recent experiments have found that both *C. chinensis* and berberine exhibited anticancer potential by inhibiting cell proliferation, induction of apoptosis, and G_2/M cell cycle arrest. At the molecular level, *C. chinensis*/berberine induced an anticancer effect through various types of molecular regulation, including inhibition of antiapoptotic protein bcl-2, activation of caspase cascade as well as the activation of Egr1-NAG-1 (nonsteroidal anti-inflammatory drug-activated

gene) proapoptotic pathway.[16] Interestingly, a recent report indicated that a newly developed long-lasting polyethylene glycol-based liposomal berberine exhibited anti-HCC potential *in vitro* and *in vivo,* further suggesting its chemopreventive effect in hepatocarcinogensis.[17]

3.3. Chrysanthemum indicum Linn.

Chrysanthemum indicum Linn. (Asteraceae) is a common CHM that has traditionally been used for the treatment of inflammation, hypertension, and neoplastic diseases in China. A recent study demonstrated that *C. indicum* Linn. extracts exhibit anti-HCC effects by attenuation of mitogenic signaling mitogen-activated protein kinase/ERK1/2 through the b2-adrenergic receptor on isoproterenol-induced growth in HepG2 and MHCC97H cells.[18]

3.4. Tanshinone IIA

Danshen (*Salvia miltiorrhiza* Radix) has widely been used in traditional CHM to treat cardiovascular and hepatic diseases. Tanshinone IIA (Tan-IIA; $C_{19}H_{18}O_3$) was extracted from *S. miltiorrhiza* Radix and its antioxidant, anti-inflammatory, and antitumor activities have been well documented in many human cancer cells. The anticancer effect of Tan-IIA was detected mainly through growth inhibition and induced apoptosis in human HCC.[19–21] It has been shown that Tan-IIA-mediated apoptosis activation and proliferation inhibition might occur through upregulated expression of stress-mediated proapoptotic proteins calreticulin, caspase-12, and GADD153.[22] More recently, several other *in vivo* studies further confirmed that Tan-IIA inhibited the growth of J5 and H22 hepatocellular xenografts, possibly by modulating the activity of proapoptotic/antiapoptotic proteins.[23,24] In addition to regulating cancer cell viability, Tan-IIA was also believed to suppress cellular metastatic activity by reducing the activity of MMP-2, MMP-9,[25] and modulating the hypoxia-inducible factor 1α-mediated epithelial–mesenchymal transition process.[26]

3.5. Solanum nigrum L.

Solanum nigrum L., a herbal plant indigenous to Southeast Asia, is a routinely administered oriental medicine. A previous study has shown that ripe fruits of *S. nigrum* L. induced growth inhibition and apoptosis in breast cancer cells.[27] A number of studies have shown that *S. nigrum* L. polyphenolic extract (SNPE) induces elevated cell cycle arrest, increased autophagy, and upregulated apoptosis in HCC cells.[28,29] At the molecular level, SNPE attenuated cell cycle regulators Cdc25A, Cdc25B, and Cdc25C; apoptosis mediators caspase-3, caspase-8, and caspase-9; as well as Bcl-2 family proteins both *in vitro* and *in vivo*.[30]

3.6. Tetrandrine

Tetrandrine is a bisbenzylisoquinoline alkaloid isolated from the roots of Radix *Stephaniae tetrandrae* S. Moore. Radix *S. tetrandrae* S. Moore is an ancient ingredient of traditional CHM and is broadly used in China to treat patients with arthritis, hypertension, inflammation, and even silicosis.[31] It was shown that tetrandrine achieves symptom relief through a pharmacological mechanism in which tetrandrine blocks Ca^{2+} channels; in addition, tetrandrine has immunosuppressive property, free-radical scavenging effects, and antiproliferative features.[32] Moreover, it was reported that administration of tetrandrine led to G_1 phase cell cycle arrest and induced apoptosis in many cancer cells through the inhibition of pro-proliferative ERK signaling.[33,34] The treatment of liver cancer cells with tetrandrine altered their morphology, induced chromatin fragmentation, and stimulated caspase activity. Interestingly, tetrandrine administration also induced intracellular accumulation of reactive oxygen species (ROS), whereas ROS scavengers, such as *N*-acetyl-l-cysteine and glutathione (GSH), completely abolished tetrandrine-induced apoptosis suggesting that ROS generation plays an important role in tetrandrine-mediated apoptosis. Furthermore, downstream Akt-associated apoptotic activity was upregulated in response to ROS generation, which indicates a possible molecular cascade for tetrandrine-mediated anticancer effect. Taken together, these findings suggest that tetrandrine could serve as an ROS/Akt regulator and could be implicated for HCC treatment.[35] Furthermore, tetrandrine also exhibited an anti-HCC effect *in vivo*. It has been shown that paclitaxel/tetrandrine co-loaded nanoparticles could efficiently repress tumor growth,[36] whereas accumulated ROS and increased autophagy were detected in Huh7 xenografts that lead to decreased tumor volume in response to tetrandrine treatment.[37]

3.7. Andrographolide

Andrographis paniculata has been a CHM for the treatment of respiratory infection, fever, bacterial dysentery, and diarrhea in many Asian countries for centuries. Andrographolide (*ANDRO*), an active compound isolated from *A. paniculata,* is known to possess various physiological regulatory characteristics such as anti-inflammatory, antibacterial, and hepatoprotection. *ANDRO* inhibited the growth of hepatoma cells by activation of c-Jun NH_2-terminal kinase (JNK) and reduction of GSH levels.[38,39] *ANDRO* also caused ROS-stimulated cycle arrest leading to the hypothesized crosstalk between JNK activation, cellular GSH homeostasis, and cytotoxicity in hepatoma cells.[40,41]

3.8. Gamboge

Gamboge is also a traditional CHM used for hundreds of years. Its major compounds gambogic acid (GA) and gambogenic acid are isolated from *Garcinia hanburyi,* and have been shown to have antiproliferative effects in HCC cell lines. In addition, it was also found that 1,3,6,7-tetrahydroxyxanthone (TTA), a xanthone derivative from *Goodyera oblongifolia*, could be a potent apoptosis inducer in HCC cells. Previous studies have demonstrated that TTA suppressed HCC through upregulated gene expression of p16

and 14-3-3.[42] The *in vivo* anti-HCC activity of GA was also made evident by the decreased size of SMMC-7721 xenotransplanted tumor in mice, possibly through the inhibition of telomerase activity.[43]

3.9. *Cornus officinalis*

Cornus officinalis Sieb. et Zucc. (Cornaceae) is another widely used CHM, with antineoplasm and anti-inflammation activities. Extracts of *C. officinalis* Sieb. et Zucc. could also downregulate lipid peroxidation resulting in hepatoprotection.[44] Regarding its anticancer effect, previous studies found that extracts of *C. officinalis* Sieb. et Zucc. exhibited a dose-dependent suppression of mutant p53 and Ras-mediated oncogenic progression and inhibited oxidative stress by scavenging free radicals against HCC cells, making *C. officinalis* Sieb. et Zucc. an effective chemopreventive agent against HCC.[44]

3.10. Curcumin

Curcumin is one of the major phenolic agents in the spice turmeric (*Curcuma longa*). There are three major curcuminoids that constitute curcumin, which are as follows: curcumin (curcumin I, 75%), demethoxycurcumin (curcumin II, 20%), and bisdemethoxycurcumin (curcumin III, 5%).[45] Although curcumin is not a traditional CHM, it has been considered as a chemoprevention agent that could suppress neoplasias, inflammation, viral infection, oxidative stress, and human immunodeficiency virus-mediated pathology for centuries.[46] A number of studies have demonstrated that curcumin could induce G_2/M phase cell cycle arrest,[47] inhibit proliferation,[48] induce apoptosis,[49] and suppress angiogenesis and metastasis[50] in different HCC cell lines. Furthermore, using *in vivo* models, the anticancer activity of curcumin was also documented indicating that curcumin could effectively reduce cancer cell multiplicity,[51] attenuate tumor growth,[52] decrease telomerase activity, prevent tumor angiogenesis, and inhibit intrahepatic metastasis.[53]

3.11. Resveratrol

Resveratrol (*trans*-3,5,4′-trihydroxystilbene) is a natural antioxidant polyphenol compound that can be found in a wide variety plants including grapes, peanuts, and berries, and could also be isolated from the dried roots of CHM *Polygonum*

Table 1
Anti-HCC effects of CHM.

CHM/compounds	For initiation	For survival/proliferation	For angiogenesis/metastasis
Scutellaria baicalensis	G_2/M phase arrest ↓ topoisomerase II (*in vitro*)[12]	↓ p53, ETS1, Cdc25B, p63, EGFR, ERK1/2, XIAP, HIF-2α, and Cdc25C; ↑ Cyclin E (*in vitro*)[13] ↓ HepG2 xenograft tumor size (*in vivo*)[15]	↓ ERK signaling ↓ MMP-2, MMP-9, and uPA (*in vitro*)[14]
Berberine/*Coptis chinensis*	G_2/M phase arrest (*in vitro*)[15]	↓ Bcl-2; ↑ Activation of procaspase-3 and procaspase-9, and NAG-1 protein (*in vitro*)[15] ↓ HepG2 xenograft tumor size (*in vivo*)[17]	
Chrysanthemum indicum Linn.			↓ MAPK/ERK1/2 signaling (*in vitro*)[18]
Tanshinone IIA (*Salvia miltiorrhiza* Radix)	G_2/M phase arrest (*in vitro*)[19–21]	↓ Bcl-2 ↑ p53, p21, Bax, calreticulin, caspase 12, and GADD153 (*in vitro*)[19,21,22] ↓ J5/H22 xenograft tumor size (*in vivo*)[23,24]	↓ EGF and EGFR (*in vitro*)[20] ↓ MMP-2, MMP-9 ↓ HIF-1α-mediated EMT (*in vivo*)[25,26]
Solanum nigrum L.	G_2/M phase arrest (*in vitro*)[27–29]	↓ Cdc25A, Cdc25B, Cdc25C;↓ Bcl-2 (*in vitro*)[30] ↓ HepG2 xenograft tumor size (*in vivo*)[30]	
Tetrandrine		↑ ROS;↓ Akt pathway (*in vitro*)[35] ↑ ROS; ↑ Autophagy ↓ Huh7 xenograft tumor size (*in vivo*)[37]	
Andrographolide		↑ ROS and JNK ↓ Glutathione level (*in vitro*)[39–41]	
Gamboge		↑ p16; 14-3-3σ gene expression (*in vitro*)[42] ↓ SMMC-7721 xenograft tumor growth ↓ Telomerase activity (*in vivo*)[43]	
Cornus officinalis Sieb. et Zucc.		↓ p53 and Ras mutation (*in vitro*)[44]	
Curcumin	G_2/M phase arrest (*in vitro*)[47]	↑ Telomerase activity; mitochondrial and nuclear DNA damage (*in vitro*)[48] ↑ 8-OHdG; ↑ ROS (*in vitro*)[50]	↓ HIF-1α and VEGF (*in vivo*)[51,53] ↓ MMP-9 (*in vivo*)[52]
Resveratrol	G_1/S phase arrest (*in vitro*)[56]	↓ Cyclin D1, p38, and Akt; ↑ p53, p21, caspase 2,3, 8, and 10, and DNA fragmentation (*in vitro*)[57]	↓ HIF-1α, VEGF, JNK1/2, SP-1 DNA, NF-κB, VEGF, and uPA (*in vitro*)[58]

8-OHdG = 8-hydroxy-2′-deoxyguanosine; CHM = Chinese herbal medicine; EGF = epidermal growth factor; EGFR = epidermal growth factor receptor; EMT = epithelial–mesenchymal transition; ERK = extracellular signal-regulated kinase; HIF-1α = hypoxia-inducible factor 1α; HIF-2α = hypoxia-inducible factor 2α; JNK = c-Jun NH_2-terminal kinase; MAPK = mitogen-activated protein kinase; MMP = matrix metallopeptidase; NF-κB = nuclear factor-κB; ROS = reactive oxygen species; uPA = urokinase-type plasminogen activator; VEGF = vascular endothelial growth factor; XIAP = X-linked inhibitor of apoptosis protein.

cuspidatum Sieb. et Zucc.[54] Recent studies have found that resveratrol can prevent or slow the progression of a wide variety of tumors including HCC.[55] At the molecular level, resveratrol inhibited cell growth through G_1 phase cell cycle arrest and increased the expression of inducible nitric oxide synthase (NOS) and endothelial NOS.[56] Resveratrol was also suggested to induce apoptosis by the activation of caspase-2, -8, and -10.[57] In addition, treatment with resveratrol significantly inhibited cell migration and invasion leading to suppression of metastasis.[58]

In conclusion an overview of anticancer effects of the aforementioned traditional CHM is summarized in Table 1.[12−15,17−30,35,37,39−44,47,48,50−53,56−58] While CHMs have been routinely applied in Eastern Asia and are increasingly common worldwide, if and when its many antitumor aspects are fully evaluated, CHM could become an ideal new alternative "medication" against HCC considering its low toxicity and high activity.[59−61] With regard to the therapeutic aspects, CHM has been proposed to be active against HCC initiation, survival, proliferation, angiogenesis, and metastasis using various *in vitro* and *in vivo* models. Furthermore, CHM could also synergistically enhance HCC inhibition and immune function as well as reduce the toxic effects when combined with radiotherapy, chemotherapy, and TACE.[62] Taken together, although it is clear that many CHMs possess excellent anticancer activity, evaluating the clinical applications of CHM using randomized, controlled clinical cohorts of liver cancer patients is still required.

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