Original Article

Traditional Chinese medicine as complementary treatment for hepatocellular carcinoma

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Abstract

Background: Hepatocellular carcinoma is an extremely recurrent and very malignant tumour. It is also the most common liver malignancy. The efficient treatment of the disease is hindered by high metastasis, recurrence rate, and drug resistance. Recent studies have shown a strong association between the malignant hepatocellular carcinoma phenotype and cancer stem cells. The treatment of squamous cell carcinoma is an important control strategy. Recurrence and metastasis of advanced liver cancers were reported to be abated by conventional Chinese medicine and traditional Chinese medicine compounds or extracts with anti-cancer stem cell activity.

Objective: The aim of this review is to examine the role of extracts used in traditional Chinese medicine to treat cancer stem cells and hepatocellular carcinoma.

Methods: In this review of scientific literatures proved that some novel chemical formulas such as monocarboxylate transporters (MCT) derived compounds are reported to inhibit squamous cell carcinoma and hepatocellular carcinoma. This review may contribute to the development of a new cancer therapy tool, particularly for the treatment of liver cancer.

Results: The current study highlighted the global scenario of Chinese medicine research on Hepatocellular carcinoma. This review will provide interesting results in terms of more health policy devolution to address existing health challenges.

Conclusions: The prognostics and survival rate of patients with hepatocellular carcinomas may be enhanced by targeted treatment of this major cell population. Traditional Chinese medicine has shown benefits to both tumour progression and drug resistance, as well as to the prevention of recurrence and metastasis. [*Ethiop. J. Health Dev.* 2021; 35(4): 320-327]

Key words: Hepatocellular carcinoma, Chinese medicine, herbal treatment, squamous cell carcinoma, cancer stem cells.

Introduction

Hepatocellular carcinoma (HCC) is one of the leading malignant tumours in China, and the second leading cause of cancer death worldwide (1,2). Every year, approximately 750,000 new HCC cases are reported globally (3). The prevalence of HCC has increased rapidly in the United States and other developed countries (3). HCC is characterized by aggressive tumours that mostly arise from metastases and postoperative recurrence (4).

Surgical resection, embolization, ablation and chemotherapy are central to the treatment of liver cancer. However, chemical compounds used in chemotherapy are generally reduced because they show some toxic effects, severe chemical resistance, and side effects and complexity. Given the grim forecast of liver cancer and the minimal alternative drugs to surgery, patients are pursuing alternative therapies to boost quality of life or survival. Complementary and alternative medicines (CAMs) can be developed to increase the efficacy of anti-cancer medicines and minimize toxicity or side effects. Traditional Chinese medicine (TCM) is one of the most common types of CAM worldwide and is widely used to treat cancer, especially using Chinese herbal medicine (CHM) (5). China has a long tradition of treating liver cancer and other malignant tumours using TCM. TCM and chemotherapy jointly can reduce adverse events, including leukopenia, thrombocytopenia, anaemia or erythropenia, liver injury, and gastrointestinal discomfort in HCC patients. Chemotherapy can develop adverse health symptoms in cancer patient; this can be minimized through the application of TCM. As the detection of HCC delays due to its fast metastatic growth of HCC, surgical interventions cannot always be performed. Here, the application of TCM may increase the survival rate of HCC patients in early advance stage and can effectively stimulate the host immune response.

The Chinese theory of Yin and Yang, and five elements of wood, fire, earth, metal and water, form the basis of diagnostics and clinical care. These represent an ancient scientific principle that describes the physical universe's structure and phenomena. The theories use natural processes and regulations to analyse the physiological roles of the human body and its relationships with natural elements.

Acupuncture, Chinese medicine exercises, and Qigong are traditional therapies in Chinese medicine. CHM includes hundreds of medicinal products, most of which are herbal products, but also minerals and animal products. Different portions of CHM are popular (e.g. leaves, roots, trunks, flowers and seeds). CHM is typically paired with basic TCM-like formulas and hypotheses, including CHM for cancer therapy. The dedication to dignity and functioning of the human body in line with modern health oncology has gained growing recognition and its status in the combined treatment of liver cancer. Recent evidence suggests that

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HCC replication, invasion and metastasis can be minimized in key trials, and that HCC patients in clinical testing can increase the survival rate and overall remission rate. One of the world's most common cancers, hepatocellular carcinoma (HCC) caused almost 7.6 million deaths in 2012, 9.1% of total cancer deaths (5,6).

In 2012, 7.82 million HCC patients were diagnosed globally, of whom 7.6 million died (7), according to the epidemiological results. East Asia and Sub-Saharan Africa accounted for 80% of HCC cases, with China accounting for more than 50% of cases (6).
The principal risk factors for liver cancer include cirrhosis, chronic hepatitis B or C, alcoholic fatty liver, and non-alcoholic fatty liver (8). Radical treatment for liver cancer usually includes liver resection, liver transplant, and radiofrequency removal, but such therapies only apply to small early HCCs less than 3cm in length. Furthermore, after radical resection, the recurrence rate approaches 70% (9). Liver cancer is very resistant to a large range of chemotherapy treatments. Although prior results suggest substantial clinical efficacy in advanced liver cancer of the target medicines sorafenib ($C_{21}H_{16}ClF_3N_4O_3$) and regorafenib ($C_{21}H_{15}ClF_4N_4O_3$), long-term display of sorafenib and regorafenib sadly results in tolerance to medicinal products and eventual progression of the disease. Severe side effects may correspond with the long-term treatment of sorafenib and regorafenib in HCC. These side effects, including hand-foot syndrome disease, scalp irritation, ulcerative dermatitis, and alopecia, have a negative impact on a patient's quality of life (10,11). Recent studies have shown that malignancy, recurrence, metastasis and drug resistance are primary causes of the involvement of cancer stem cells (SCCs) (11,12). SCC theory reveals that a small portion of SCC drives tumor growth (13). SCC is considered to be capable of self-renewal and tumour differentiation, notably through the development of tumour metastases, which explains tumour recurrence observed clinically and in prospective malignancies, as well as techniques of metastasizing following chemotherapy and radio wave therapy.

The cell surface marker CD 117, CD 133, CD90 or CD44 can be used to isolate SCC from a wide range of tumours, eg from tissues and cell lines, OV6 markers, epithelial cell adhesion molecule (EpCAM) and aldehyde dehydrogenase-1 (14,15). Cell surface markers including c-kit are available for use in several tumours. Studies have found that the malignant HCC and SCC phenotype are correlated (16). As a potential treatment target for HCC, SCC currently attracts interest.

Expression and activation of EMT-inducing transcription factors occurs in response to various signalling pathways, including those mediated by transforming growth factor β (TGF-β), bone morphogenetic protein (BMP), epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), Wnt, Sonic Hedgehog (Shh), Notch, and integrin signalling (17-20).

Such abnormality encourages the autonomy, proliferation, survival and differentiation of CCS considerably (15). The epithelial cells lose their heterogeneous properties and gain mesenchymal properties, such as mobility, invasion, immune cell escape and increased apoptosis resistance. EMT is a complex mechanism of molecular and cellular retrogradation. Wnt/β-catenin activation is one of the most abnormal pathways observed in 66% of HCC in recent years. EMT is known for the production of the CSC HCC. The SCC-mediated transmission and maintenance of resistance to the SCC was stated to have an irregular Wntsignaling. The CD 133 +, EpCAM+ and OV6 + -SCC (17) define activation of the Wnt/β-catenin signal. Some studies showed that TGF-β1, by formation of EMT (15), promotes CSC-like properties. Evidence suggests that the NF-βB inhibition decreases the number of parent cells, and the capacity to generate three-dimensional culture mammals has been shown to be present in such cells (18). The JAK/STAT signalling pathway regulations in the SCC have shown to facilitate the expansion of these cancer cell systems in a robust model system (19).

China's medication has long been used for hepatic disease prevention and treatment. Clinical findings and studies in recent decades have shown good anti-cancer properties in Chinese herbal medicines as well as extracts (20,21,22). According to studies, its conventional Chinese medicinal derivatives are anti-SCC (23,24). In recent years, the side effects of Chinese medicines and its derived compounds have been addressed. These medicines are essential alternative medicines for HCC treatment.

In this article, we examine the present state of knowledge about Chinese medicinal medicines and extracts in the treatment of SCC and HCC.

Materials and methods

Scientific literature was examined in PubMed and China's National Information Infrastructure Database using key words such as 'hepatocellular carcinoma', 'cancer stem cells' and 'Chinese medicine'. A brief overview of herbal medicinal products in Chinese and its components, which have been shown to inhibit SCC in HCC, is given below.

Table 1: **Summary of Chinese herbal medicine activity against CSCs in HCC**

Chinese herbal medicine	Herbal composition	Pharmacological inhibitory effect	Reference
Brucea javanica	*B. javanica*	Drug resistance, CSC sphere, and cancer stemness	(25,26)
BRM270	*Saururus chinensis Arnebia euchroma (Royle) Johnst. Scutellaria baicalensis Citrus unshiu Markovich Portulaca oleracea Prunella vulgaris var. lilacina* Aloe vera	Drug resistance, tumor growth, cancer stemness, apoptosis, and proliferation	(27-29)
Song-you Yin	*Astragalus membranaceus Salvia miltiorrhiza Lycium barbarum* L *Crataegus pinnatifida* Bge, *Trionyx sinensis Wiegmann* Medlar Turtle shell Parched hawthorn	Growth, metastasis, drug resistance, EMT, and cancer stemness	(30-33)
Jiedu Xiaozheng Yin	*Oldenlandia diffusa P. vulgaris Pseudobulbus cremastrae Hedyotis Diffusa* Willd, *Prunella, Psuedo bulbus Cremastrae* and *Sophora flavescens*	Apoptosis, proliferation, and cancer stemness	(34)

Table 2: Summary of phytochemical activity against CSCs in HCC

Phytochemical	Source	Pharmacological inhibitory effect	Reference
Sophocarpine	*Sophora alopecuroides L.*	Proliferation, invasion, migration and cancer stemness	(33,35,36)
Epigallocatechin-3-gallate	Green tea	Proliferation and cancer stemness	(37,38)
Resveratrol	Mulberries, peanuts and grapes	Apoptosis, proliferation, drug resistance	(39,40)
Curcumin	Ginger	Apoptosis, proliferation and cancer stemness	(29,41)
Pterostilbene	Blueberry	Cell cycle arrest, apoptosis, invasion and migration, EMT, and cancer stemness	(22-27)
Baicalein	*Scutellariabaicalensis Georgi*	Autophagy, spheroid formation and cancer stemness	(33,13)
Chrysin	*Passiflora caerulea*	Migration, invasion proliferation, self-renewal and cancer stemness	(30,41)
2-Ethoxystypandrone	*Polygonum cuspidatum*	Apoptosis, proliferation and cancer stemness	(28)
Lupeol	Fruits, vegetables and herbal medicines	Tumorigenicity and drug resistance	(37,39)
Oridonin	*Rabdosiarubescens*	Self-renewal and cancer stemness	(16,27)

Note: Cancer stemness refers to the stem-cell-like phenotype of cancer cells and has been associated to many factors of hepatocarcinogenesis.

Results

Brucea javanica: *Brucea javanica* also known as Macassar kernels is a shrub in the family Simaroubaceae. The specific epithet *javanica* is from the Latin, meaning "of Java". Other common names in English include Java brucea and kosam. It was first reported in the 'Classic Chinese Medicine Pharmacopoeia' (38). *Bacillus javanicus* can be used to Clear heat and detoxify, removes lung hotnes, eradicate malaria, and resolve phlegm, according to the theory of Chinese medicine. Numerous experiments in the last few decades have verified *Bacillus javanicus*' anti-cancer properties.

BRM270: BRM270 is a natural compound made from seven herbal plant (*Saururus chinensis, Citrus unshiu Markovich, Aloe vera, Arnebia euchroma, Portulaca oleracea, Prunella vulgaris var.lilacina* and *Scutellaria bacicalensis*) extracts used in Asian traditional medicine and has the potential to target CSCs. Several studies have demonstrated the positive effects of BRM270 against chemoresistant cancer and its synergy alongside existing cancer drugs, including paclitaxel and gefitinib. (27).

Song-you Yin (SYY): Songyou Yin (SYY) is a traditional Chinese medicine (TCM) and contains 5 herbal compounds. Our team's previous study verified the effectiveness of treatment of HCC in vivo and in vitro. SYY effectively inhibited tumour growth, metastasis, and prolonged survival in nude mice models. Moreover, regarding resistance to chemotherapy, SYY enhanced HCC sensitivity to oxaliplatin through inhibition of stemness or reverse EMT. Based on the above-mentioned evidence, we proposed the hypothesis that SYY could play a role in minimizing the pro-metastatic effects of insufficient RFA in HCC, particularly when combined with IFN-α. (30).

Jiedu Xiaozheng Yin (JXY): *Jiedu Xiaozheng Yin* (JXY), a polyherbal formula of TCM, consists of the following herbs *Hedyotis diffusa, Pseudobulbus Cremastrae seu Pleiones, Spica Prunellae* and *Radix Sophorae Flavescentis*. All four medications are for cancer.

Sophocarpine: Sophocarpine is a tetra-cyclic alkaloid and one of *Sophora alopecuroides* L.'s more common active ingredients. Sophocarpine is used for treatment of cancer, inflammation, and viral and arrythmic infection (35,39).

Epigallocatechin-3-gallate (EGCG): The key active and water-soluble component of green tea is epigallocatechin-3-gallate (EGCG), a natural phenol compound of catechins. Many studies have shown that EGCG and green tea extract can help prevent tumors in different rodent organs. Bioavailability, fast and easy absorption and fewer side effects make EGCG a miraculous anti-cancer agent. High EGCG is found in green tea (7380mg/100g) compared to white tea and black tea. The Wnt/β-catenin signalling pathway responds well with the apoptosis of colorectal cancer cell-mediated liver metastasis (37,42).

Resveratrol: Resveratrol is a naturally occurring phytochemical present in wine, grapes, berries, chocolate, and peanuts and exhibits numerous pharmacological properties to treat a variety of ailments (30). It is generally used for the prevention of cardiac disorders, cancer and other age-related diseases (29). Resveratrol, by activating caspase-3/7, induces pancreatic SCC apoptosis, and inhibited Bcl-2 and XIAP expression. The pancreatic SCC inhibits resveratrol, by interaction with the CSC pluripotency (Nanog, Sox-2, c-Myc& Oct-4) factors and the ABCG2 resistance gene, and interferes with the formation of automatic self-renewal and sphere of EMT markers (Zeb-1, Slug and Eg) (39).

Curcumin: Curcumin, a yellow polyphenolic pigment from the *Curcuma longa* L. (turmeric) rhizome, has been used for centuries for culinary and food colouring purposes, and as an ingredient for various medicinal preparations, widely used in Ayurveda and Chinese medicine. It is an acidic material of polyphenol and a principal chain is an aliphatic-aromatic unsaturated group. Curcumin is commonly used for its anti-cancer properties (29).

Pterostilbene*:* Pterostilbene (trans-3, 5-dimethoxy-4-hydroxystilbene) is a natural dietary compound and the primary antioxidant component of blueberries. (39). The antioxidant activity of pterostilbene has been implicated in anticarcinogenesis, modulation of neurological disease, anti-inflammation, attenuation of vascular disease, and amelioration of diabetes. A number of studies have shown that pterostile plain can lead to cell cycle arrest and apoptosis in various cell lines, including hepatic cell cancer. (33-35).

Baicalein: Baicalein (5,6,7-trihydroxyflavone), a flavonoid extracted from the roots of *Scutellaria baicalensis* and *Scutellaria lateriflora*, is widely used in the treatment of inflammation, coronary disorders, respiratory and gastrointestinal infections. (40-41). A recent study (33) showed that flavin can induce blocks of G0/G1 by inhibiting AKT and promoting β-catenin and cycline D1 degradation in HCC cells. In an HCC xenograft patient model, baicalein can inhibit mammalian becalming rapamycin C1 (mTORC1) induced autophagy and interact with m133 to stop stem cell formation and cell death due to the formation of Huh7 sphere of CD133 + (38).

Chrysin

Chrysin, also called 5, 7-dihydroxyflavone, is a flavone found in honey, *propolis, the passion flowers, Passiflora caerulea* and Passiflora incarnata, and in *Oroxylum indicum.* It is extracted from various plants, such as the blue passion flower (*Passiflora caerulea*). The combined effect in micellar formulations of docetaxel and Fibrin glue has a synergistic effect in SCC, inhibiting the *in vitro* migration rate of SCC (36). The new synthetic analogue of 8-bromo-7-methoxychrizine, CD133 + spherical cells and CD44 of

hepatic cancer stem cells, *in vitro* and *in vivo*, has reportedly inhibited their propagation and self-renewal (38, 39). Chrysin protein and sorafenib in combination have a synergistic impact on the existence of stem cells from liver cancer (37).

2-Ethoxystypandrone: *Polygonum cuspidatum* in Chinese medicine has excellent anti-cancer activity with its active ingredients, including resveratrol (39).

Oridonin: Oridonin is a rhodiola-isolated active diterpene that has been used extensively for long-term cancer and other diseases The P53 gene activity, commonly known as a tumour-suppressor gene, has been induced by oridonin therapy. Thus, the cell cycle arrests the tumour progression through its target specific cell cycle arrest mechanism (38).

Lupeol: Lupeol, is found in vegetables such as white cabbage, pepper, cucumber, tomato, in fruits such as olive, fig, mango, strawberry, red grapes and in medicinal plants such as American ginseng, Shea butter plant, *Tamarindus indica, Allanblackia monticola, Himatanthus sucuuba*, *Celastrus paniculatus, Zanthoxylum riedelianum*, *Leptadenia hastata, Crataeva nurvala, Bombax ceiba and Sebastiania adenophora* used by native people in North America, Latin America , Japan, China, Africa and Caribbean islands. Paclitaxel and platinum combination therapy can be used to treat cancer (13,38). Furthermore, lupeol not only inhibits the ability to renew HCC cell lines and HCC-clinical samples that cause hepatic cancer, but also inhibits cancer and expression of CD133 (41).

Discussion

According to a study by Liao *et al.*, Chinese herbs can be effectively used for antioxidant activity and thus for measuring the radical scavenging capacity of biological samples by oxygen radical absorbance capacity (ORAC) assay (43). The study analysed 45 herbs used in TCM, and the results showed that they had a wide range of antioxidant activity, which may play a key role in treating HCC (43). As an inhibitor of central factor 2 relative to erythroid cells (Nrf2), a significant regulator of cellular antioxidant systems, sinapine (one of *B. javanica*'s active components) can increase the efficacy of chemotherapy. Nrf2 participates in other defence mechanisms mediated by SCC, survival rate and stress tolerance, which suggests that brusatol activity can help reverse drug resistance (25). Furthermore, the extract of *Bacillus javanicus* was found to effectively inhibit the production of CSC percolations. *Bacillus javanicus* extract has altered the expression of HCC cell markers Nanog, CD133 and EpCAM. One study shows that the adjuvant therapy of *Bacillus javanicus* can be used and the residual drug-resistant SCC can be removed (26).

Isoflavones are highly similar in structure to 17β-estradiol, so that they may act as an agonist to estrogen. Estrogen can inhibit the expression of interleukin-6 (IL-6); this may result in the proliferation of tumor cells and apoptosis resistance. This anti-estrogenic effect consumption of isoflavone from a natural soy diet may not be suitable for women suffering from hepatitis B and hepatitis C virus infection. Therefore, the use of TCM may positively influence the HCC treatment.

Studies have found that BRM270 is a bacteriolytic activator and an important cancer cell apoptosis agent. Jeon *et al.* (28) demonstrate that *in vivo* and *in vitro*, BRM270 can inhibit cell and cell line development. Combining BRM270, radiation and chemotherapy, the survival rate of mice can increase dramatically, and tumour growth can be inhibited. One of SCC's hallmarks is multidrug resistance. It also exhibits a big effect inhibiting Dox-resistant tumours (doxorubicin or Dox). To overcome Dox-resistance, individual microRNA (miRNA) expression profiling technology is used as the current treatment to overcome Dox resistance in HCC patients (27). BRM270 prevents a G2, M, cell cycle within the CD133 + population of cancer stem cells. Research by Kumar *et al.* (40) showed the impact of BRM270 on human expression of CD133 + HepG2 and SNU-398 stem-cell disease. Treatment with BRM270 has been shown to reduce the rate of proliferation and simultaneously cause apoptosis in liver injuries, preventing cancer progression. In addition, BRM270 increases the HCC stem cell survival rate substantially and decreases c-Myc, Bcl-2 and c-Jun expressions. Studies have found that by downregulating the C-Jun Apoptosis Pathway regulated by Cyclin D1/Bcl-2, BRM270 can effectively inhibit the proliferation and apoptosis of liver cell cancer cells (40), suggesting that BRM270 has the potential to treat HCC.

Furthermore, Jia *et al.* (31) found that the chemosensitivity to oxaliplatin of MHCC97H and HepG2 is substantially increased during the initial SYY procedure. Together with oxaliplatin and SYY therapy, tumour size and lung metastases can dramatically decrease and enhance survival.

The CSC-related markings CD90, CD24, and EpCAM (31) were decreased with treatment with SYY. Zhang et al. (32) found that swimming exercise increased CD4/CD8 peripheral blood CYS and decreased TGF-β1 in peripheral serum blood, spleen, and HCC patients' tumour tissues. EMT is a good CTS starting signal. The effect of SYY on EMT was evaluated by another study (33). The results show that MHCC97H SYY cells can inhibit morphological changes caused by TGF-β1 considerably before treatment and reverse the expression of E-cadherin and n-cadherin EMT markers. Additional studies have shown that SYY inhibits EMT by attenuating the TGF-β1 expressions and inhibiting noradrenergic homology phosphorylation 2 and 3 in the Dam (33).

Liu *et al.* have shown that JXY can cause the arrest and apoptosis of HCC cells and inhibit the spread of NF-ȚB cells. By inhibiting Bmi1 and Wnt/β-catenin signaling pathways, JXY partly inhibits the spread of HCC. JXY inhibiting the expression of c-kit and CD133, thus inhibiting SCC in the HCC mouse (34).

A recent study (36) shows that sophocarpine can decrease HCC viability, remove HCC and reverse the malignant HCC cell phenotype. The level of CSC can also be reduced and tumour formation inhibited. It is suggested that sophocarpine's activity mechanism is to negatively regulate the activities of the signaling pathway for Akt/GSK3β/B-Catenin? glycogen synthase and inhibit the exertion of anti-tumor effects for EMT-induced TGF-b.

EGCG, along with regular chemotherapy, can be a useful chemo preventive for CSC-HCC. EGCG controls the mRNA expression of the CD133 adenosine triphosphate tapestry, the Nanog, the C1 subfamily, and the adenosine triphosphate tapestry binding subfamily, the G2 subfamily (ABCG2). In addition, Wnt signals may be effectively impeded by EGCG (29).

Resveratrol has shown that the HGF-c-Met signalling pathway is modified negatively to exercise a profound anti-tumour effect on human HCC cells. In addition to a large number of anchoring-based HCC cells, the dose-dependent growth of HCC-CSC was also inhibited by resveratrol. Short-term resveratrol exposure can reduce the activation of HGF-induced c-Met signalling pathway and long-term exposure can interfere with the expression of c-Met plasma membrane. Resveratrol thus inhibits HGF-induced cell invasion (40). Resveratrol in HCC is believed to affect CSC through the Wnt signal route.

The combination of curcumin and EGCG was found by Chung *et al.* (40) to adversely regulate STAT3-NF-jB signals by decreasing the number of cancer cells in the case of CD44 + and inhibiting the CSC phenotype. Marquardt *et al.* (38) reported that curcumin can inject carcinogenic NF-JB signalling effectively and can decrease the characteristics of strains of liver cancer. Curcumin is responsible for selective SCC depletion that occurs with reduced bead size, reduced bead formation, modified SCC markers and suppressed carcinogenicity (40). These findings show that curcumin is an option to treat HCC by stem cells.

Lee *et al.* (27) have shown that, by reducing markers C-MyC, cyclooxygenase 2, and EMT (for example vimentin and Twist1), it can inhibit radiation-induced accumulation for CD133 + sub-populations in Mahlav HCC cells. As an anti-CSC agent, terpenes can be used to prevent HCC development.

Recently researchers have found that the STAT3 activation has been seriously blocked by 2-ethoxystipandrone, a recent Juglan analogue detected by the root extract of *Polygonum cuspidatum* in ethyl acetate. It triggers apoptosis and impedes HCC and HCC-CSC cell proliferation (38). 2-ethoxystanpanone may therefore be a promising compound that can produce anti-CSC medicines in addition to its role as a signal inhibitor for STAT3.

Recent research shows that Rubescensine A can make arsenic trioxide-responsive HCC cells (As2O3), which can help optimize HCC therapy for patients with As_2O_3 (39). Furthermore, Rubescensine A synergistically improves the ability of JQ1 (a terminal extra domain and bromine domain inhibitor) to inhibit cell viability, considerably increasing the HCC and CSC cell apoptosis inducted by Jq1 (41).

Conclusions

SCC plays a key role in HCC invasion and metastasis, treatment resistance, and recurrence. Thus, the prognostics and survival rate of HCC patients may be enhanced by targeted treatment of this major cell population. TCM has shown benefits to both tumour progression and drug resistance, as well as to the prevention of recurrence and metastasis. More and more research has shown the ability of Chinese herbal products or herbal compounds to substantially inhibit SCC. For example, the CSC HepG2 cell population increased in one of our studies. Long-term incubation with the chemical therapy medicine paclitaxel prevented this increase. CSC HepG2 cell population increased. The result is that TCM extract and paclitaxel treatment for HCC cells resulted in substantially smaller tumour development and recurrence than paclitaxel or vehicle-specific HCC cells. Since it has been demonstrated that many Chinese medicines or components control SCC pathways, including Wnt/β-catenin, more medicinal drugs derived from Chinese medicines may inhibit cancer absorption. This is why combining TCM therapy and chemotherapy or other therapies derived from TCM can provide an effective way to battle HCC.

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