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Review Article

# Research Progress on the Effect of Traditional Chinese Medicine Monomers and Derived Compounds on Liver Cancer Stem Cells

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## Abstract

Hepatocellular carcinoma (HCC) is the most common malignant tumor in the world with a high mortality rate. Liver cancer stem cells (LCSCs) are a small part of HCC cells with the abilities of self-renewal, proliferation, differentiation and tumorigenesis, which may be the main reasons for the high drug resistance and recurrence rate of HCC. Therefore, targeting LCSCs has become an effective way to cure HCC. A lot of evidences show that traditional Chinese medicine (TCM) plays an extremely important role in the prevention and treatment of HCC as an alternative or complementary therapy. In recent years, an increasing number of studies have shown that TCM monomer extracts and their derived compounds target LCSCs through a variety of pathways, providing new ideas for the treatment of liver cancer.

**Keywords:** Traditional Chinese medicine; Monomers; Derivatives; Liver cancer stem cells; Hepatocellular carcinoma

## Introduction

Hepatocellular carcinoma (HCC) is the most common malignant cancer all over the world, accounting for about 75% ~ 85% of primary liver cancer. It is the third leading cause of cancer-related mortality with a poor prognosis [1,2]. HCC can be caused by chronic hepatitis virus (HBV, HCV) infection, aflatoxin exposure, excessive alcohol consumption, obesity and other reasons, whereas in China, chronic HBV infection is one of the key factors for the incidence of HCC [1].

Liver cancer stem cells (LCSCs) are considered to possess stem cell-like properties in HCC. And many surface markers of LCSCs have been identified, such as EpCAM, CD133, CD44, CD13, CD90, CD24, CD47, OV6, K19, C-KIT, ABCG2 and ALDH, etc. LCSCs are also characterized by infinite self-renewal, in vivo tumorigenicity, subsequent generation of differentiated progeny recapitulating the parental tumor phenotype, the ability to form sphere and so on, which are closely related to the stemness, metastasis, recurrence and therapeutic resistance of HCC [3,4]. In addition, Side Population cells (SP) can also be used to identify LCSCs and is associated with the chemotherapy resistance of HCC [5]. They are also regulated by multiple signaling pathways, such as the classical Wnt/β-catenin, Notch, TGF-β, IL-6/STAT3and PI3K/Akt/mTOR signaling pathways [4,6].

Traditional Chinese medicine (TCM), as an important treatment of China, has been used to prevent and treat lots of diseases for thousands of years. With the increasing attention and studies on TCM, researchers have found that TCM monomer extracts and their derivatives can exert outstanding anti-hepatocarcinogenic effect through myriad mechanisms [7,8]. In recent years, a growing number of studies have shown that TCM monomers and their derivatives play an extremely important role in the regulation of LCSCs, which are potential targets for

the treatment of HCC, including inhibiting their proliferation and promoting their apoptosis [9,10]. Here, we have summarized the effects of TCM monomers and their derivatives on LCSCs and their mechanisms in the past ten years, so as to provide new ideas and methods for the treatment of HCC.

## TCM Monomers Inhibit LCSCs

### TCM monomers regulate LCSCs-related signaling pathways

#### Wnt signaling pathway

The classical Wnt signaling pathway enhances the expression of CSCs markers and the ability of self-renewal, which is of great significance for the maintenance of CSCs stemness [11]. Casticin (CAS), which is derived from Fructus Viticis Simplicifoliae，decreased the expression level of β-catenin and its downstream target CyclinD1 in LCSCs, and inhibited cell self-renewal. Moreover, the Wnt/β-catenin agonist lithium chloride could reverse this effect, demonstrating that CAS inhibits LCSCs by blocking the Wnt/β-catenin signaling pathway [12]. Amarogentin, a secoiridoid glycosidic compound which is extracted from Swertia chirata, notably suppressed the expression of β-catenin, phosphorylated β-catenin, Gli1, Sonic Hedgehog ligand as well as SMO, and up-regulated the expression of PTCH1 in CD44+ LCSCs [13]. Additionally, epigallocatechin gallate (EGCG) in green tea could reduce the number of CD44+ LCSCs, and in this process, Wnt/β-catenin, Hh/Gli1 and their related genes Cyclin D1, c-Myc and EGFR up-regulated, while the expression of E-cadherin down-regulated [14]. Amarogentin as well as EGCG may regulate LCSCs by modulating self-renewal Wnt and Hh pathways. Ovatodiolide, a macrocyclic diterpenoid which is isolated from the TCM herb Anisomeles indica, induced the down-regulation of β-catenin and its downstream effect genes and prevented hepatospheres formation, thereby inhibiting liver cancer stem cell-like properties via Wnt/β-catenin pathway [15]. Gynura divaricata (GD) belongs to Compositae family and has long been used in the treatment of liver diseases such as hepatitis and liver cancer. GD extracts down-regulated the activity of Wnt reporter gene and the expression of Wnt target genes Cyclin D1, c-Myc and AXIN2, meanwhile, up-regulated the expression of E-cadherin, then targeted LCSCs through Wnt pathway [16].

#### PI3K/AKT Signaling Pathway

PI3K/AKT pathway is involved in the occurrence and progression of various types of cancers comprising HCC, and it is also an important signaling mechanism in the regulation of LCSCs[6].ψ-Bufarenogin is a novel bioactive compound which is isolated and identified from toad skin with less side effects that has a strong inhibitory effect on HCC[17]. After pretreated with ψ-Bufarenogin, the phosphorylation of Akt were suppressed in a dose-dependent manner without affecting the expression of STAT3. Then, the inhibition of stemness regulators MCL1 and SOX2 could be blocked by the overexpression of dominant negative mutant Akt (DN-Akt), indicating that PI3-K/AKT pathway may be involved in the inhibition of proliferation of LCSCs by ψ-Bufarenogin [18]. As a kind of polyphenols existing in Rhizoma curcumae longae, curcumin has a prominent anti-tumor property [19]. It significantly reduced the protein levels of PI3K, p-AKT and p-mTOR, and PI3K/AKT activator reversed the inhibitory effect of curcumin. These results prove that curcumin inhibits the growth of LCSCs through PI3K/Akt/mTOR signaling pathway [20]. Docetaxel, a complex diterpene molecule originally isolated from the needles of the European yew (Taxus baccata), could reduce the expression of p-Akt and SOX2 in LCSCs [21]. But after blocking the PI3K/Akt signaling pathway with LY294002, its inhibitory effects were partially limited, suggesting that docetaxel may promote the apoptosis of LCSCs by restraining the PI3K/Akt signaling pathway [22]. Sophorine, a quinolizine alkaloid which is extracted from Sophora alopecuroides Linn, could observably suppress the PI3K/Akt pathway, decrease the expression levels of p-Akt, p-GSK-3β and p-β-catenin in cells, and inhibit LCSCs by regulating the Akt/GSK-3β/β-catenin axis [23]. Futhermore, some studies have found that as a tumor suppressor gene, PTEN can regulate the activity of ABCG2 through the PI3-K/Akt pathway, thus targeting CSCs [24]. Lupanol, a natural triterpenoid, could increase the PTEN level in LCSCs and continuously decrease the expression levels of phosphorylated Aktser473 and ABCG2. After knocking down the PTEN, the inhibitory effect on the ability of primary spheres to form secondary spheres significantly diminished [25].

#### JAK2/STAT3 signaling pathway

JAK2/STAT3 signaling pathway can induce the effects of multifarious growth factors and cytokines, which is closely related to the occurrence and development of many kinds of cancers. And the abnormal activation of JAK2/STAT3 signaling pathway in multiple CSCs can promote the occurrence of tumors [26]. Silybinin is a flavonoid which is extracted from silymarin seeds. When combined with sorafenib, silybinin could inhibit the phosphorylation of STAT3 and down-regulate the expression of CSCs-related proteins KLF4, NANOG and β-catenin, and then restrained the formation and self-renewal of LCSCs [27]. Juglone analogues are active constituents with antiviral, anti-inflammatory and anti-cancer effects that can be isolated from many medicinal plants, and have STAT3 pathway inhibitory activity. Li et al. found that a juglone analogue 2-ethoxypyranone, the EtOAc extract of the *P. cuspidatum* root, inhibited the constitutive activation of STAT3 phosphorylation in HCC cells induced by IL-6, blocked the formation of tumorspheres, and dose-dependently inhibited the proliferation of LCSCs by blocking the activation of STAT3 [28]. Furthermore, cucurbitin B (CuB), a tetracyclic triterpenoid mainly isolated from Cucurbitaceae, had been proved to restrain the expression of phosphorylated p-JAK2 and phosphorylated

p-STAT3 in LCSCs and down-regulate the expression of Cyclin B1, CDK1 and CD133 in a concentration-dependent manner, thereby arrested cell cycle and stemness characteristics by suppressing the JAK2/STAT3 signaling pathway [29].

**TGF-β signaling pathway**

TGF-β regulates cell self-renewal, growth and differentiation, while Smad2 is a receptor for TGF-β. The TGF-β/Smad2 signaling pathway has been shown to be closely related to the stemness of LCSCs [30]. As an isoflavone, glabridin (GLA) is isolated from the root of *Glycyrrhiza glabra* L., and exhibits notable biological properties including anti-bacterial anti-inflammatory, anti-tumor, anti-oxidation, neuroprotective [31]. GLA could inhibit TGF-β-induced Smad2 phosphorylation and endogenous Smad2 activation, promote the expression of miR-148a in a dose and time dependent manner, finally suppressed LCSCs-like characteristics through the inhibition of miR-148a-mediated TGF-β/Smad2 signaling pathway [32]. Arsenic trioxide (ATO) is considered to be the most toxic compound in TCM and has been proved to inhibit the growth of cancer cells [33]. ATO could reduce the expression of Smad3 by promoting the expression of miR-491 in vivo and vitro. After the knockout of miR-491 or Smad3, inhibition of endogenous TGF-β signaling and CSCs-like properties diminished, demonstrating that ATO targets LCSCs by inhibiting endogenous TGF-β signaling through miR-491-mediated Smad3 silencing [34].

**NF-κB signaling pathway**

NF-κB signaling pathway is involved in a range of biological processes including cell proliferation and differentiation, it is also believed to be involved in the maintenance of many stem cells as well as CSCs, and contributes to the invasion of CSCs [35]. Curcumin treatment led to selective depletion of LCSCs in susceptible strain, which was evidenced by reduction of SP cells and sphere formation, down-regulation of CSCs markers and diminished tumorigenicity. Alternatively, this process could be enhanced by use of NF-κB inhibitors or blocking of NF-κB signaling [36]. Wang et al. found that the inhibitory effect of ATO on CD133 and EpCAM weakened in the BELMDR cells which were transfected with NF-κB siRNA. Moreover, ATO could activate miR-148A through demethylation, weaken the phosphorylation of P65, and control the NF-κB pathway, thereby inhibiting the phenotype of LCSCs [37]. Further, after ATO intervention, the expression of LIF, JAK1, STAT3 as well as NF-κB signaling pathway members P50, P52, P65, c-Rel, significantly down-regulated in LCSCs, revealing that ATO effectively induces differentiation of LCSCs by synergistic inhibition of LIF/JAK1/STAT3 and NF-κB signaling pathways [38].

**EGF/EGFR signaling pathway**

EGF is a ligand that binds to EGF receptor (EGFR), which is a member of the receptor tyrosine kinase (RTK) family. The activation of the EGF/EGFR signaling pathway is closely associated with poor prognosis of HCC [39]. It has been found that the EGF/EGFR signaling pathway plays an important role in the formation and maintenance of many CSCs [40]. Catechol is a kind of natural compounds which can be separated from natural plants [41]. Lim et al. found that the number of mammosphere increased by EGF were decreased after catechol treatment through mammosphere assay. And the same concentration of catechol and EGFR antagonist carnitinib could reduce the expression of CD44 and Nanog. Taken together, catechol can regulate the level of CSCs markers and inhibit stem cell-like characteristics through EGF/EGFR signaling pathway [42]. Moreover, Brucea javanica (BJ) water extract dose-dependently diminished the levels of EGFR and Akt, and inhibited the phosphorylation of Akts473 in Hep3B cells. It could also promote cell apoptosis and reduce the growth of LCSCs by targeting EGFR [43].

**Other relevant signaling pathways**

Bis(2-ethylhexyl) phthalate (DEHP) could increase the proportion of cancer stem cell-like cells and maintain the stemness of stem cells in vitro. While curcumin could block DEHP-induced up-regulation of AhR and phosphorylation of ERK and SK1 in vitro, and regulate LCSCs via inhibiting AHR/ERK/SK1/S1PR3 signaling pathway [44]. The number of CD133 positive cells signally decreased after the intervention of amarogentin in the HepG2 cells which possessed stemness after insufficient radiofrequency ablation (IRFA). Then the expression levels of CD133, VEGFA, DLL4 and Notch1 decreased, and the phosphorylated p53 level increased. These results suggest that amarogentin may target LCSCs through the p53-dependent VEGFA/DLL4/Notch1 pathway [45]. As traditional Chinese medicine, persimmon (Diospyros kaki L.f.) tree leaves are often used to treat chronic ulcers, and their main components are flavonoids and terpenoids, which have antioxidant, lipid-lowering, anti-inflammatory, anti-cancer and anti-allergic effects [46]. D. kaki leaves ethanol extract (EEDK) could inhibit the up-regulation of the expression of stemness markers KRT19 and CD44 induced by HGF stimulation, as well as the phosphorylation of Met and JNK, and reduced the formation of stemness characteristics of HCC cells by inhibiting HGF/Met signal transduction [47]. HH-Gli pathway is associated with numerous types of tumors and plays an important role in the differentiation of CSCs. After ATO intervention, the expression of GLI1 and its downstream target genes PTCH1 and WNT1 in CD133+ Huh7-wt cells down-regulated. It also reduced the expression of CD133 and induced differentiation of LCSCs via targeting the HH-Gli pathway [48]. Matrine, an alkaloid existing in the traditional Chinese medicine Sophora flavescens Ait, mediates anti-inflammatory, anti-tumor, antiviral and other biological effects, and is used in the treatment

of a number of diseases including cancers [49]. It inhibited the proliferation of LCSCs in a dose-dependent manner, and up-regulated the levels of CAR, laminin, E-cadherin as well as fibronectin in LCSCs which led to the reduction of cell adhesion and the increase of cell apoptosis. All in all, matrine may inhibit LCSCs by regulating CAR signal transduction [50].

### TCM monomers inhibit LCSCs-related EMT

As a component of Pterocarpus marsupium, Pterostilbene (PT) is a resveratrol analog and has lots of biological activities such as anti-inflammatory, lowering blood lipid and blood glucose [51]. PT could reduce the expression of the stem gene c-Myc in CD133+Mahavu cells, which caused the inhibition of invasion and migration abilities of cells. PT also reduced the expression of vimentin in a dose-dependent manner, down-regulated the expression of chemotaxis related molecules CXCR4 and EMT-related transcription factor Twist1, and prevented the production of LCSCs [52]. He et al. found that E-cadherin and N-cadherin up-regulated but the level of EMT-related transcription factor Twist reduced in CD133+ sphere-forming cells when treated by CAS. The EMT process was reversed, but this effect could be partially restored by overexpression of Twist, suggesting that CAS can inhibit EMT through down-regulating Twist to target LCSCs [53].

### TCM monomers up-regulate LCSCs-related miRNAs

The subcytotoxic concentration of CAS inhibited the activity and expression of DNMT1, promoted the expression of miR-148a-3p, reduced the expression of CSCs markers and the ability of sphere formation, and restrained the stemness of HCC cells by blocking the negative regulation between DNMT1 and miR-148a-3p [54]. Furthermore, isovitexin (ISOV), as a natural flavonoid compound in traditional Chinese medicine, such as Fructus viticis and Cucurbitaceae, has been found to have inhibitory effect on CSCs in osteosarcoma[55]. After ISOV treatment of SK-Hep-1 cells, the sphere and colony formation decreased, the expression level of CSCs markers down-regulated, while the level of miR-34a up-regulated. In other words, ISOV inhibits the stemness of HCC cells via regulating miR-34a[56].

### TCM monomers inhibit the expression of LCSCs-related oncogenes

#### BMI1

As an oncogene, BMI1 plays a crucial role in the self-renewal of stem cells and is associated with a lot of tumors [57]. Kaneta et al. obtained the Wallichoside which was isolated from the methanol extracts of Beaumontia murtonii and Eugenia operculata. the Wallichoside could inhibit the sphere formation of Huh7 hepatocellular and reduce the number of EpCAM-positive Huh7 cells, thus affected the growth or renewal of LCSCs by inhibiting the expression of BMI1 [58].

#### YAP-1

YAP-1 is an essential carcinogenic gene in HCC, which participates in EMT of tumor cells and promotes cell proliferation [59]. Chang et al. found that ovatodiolide reduced the expression of YAP-1 protein in SP cells in a dose-dependent manner. And ovatodiolide also down-regulated the expression of Sox2 and Oct4, dramatically inhibited the self-renewal of LCSCs in vitro, and modulated the LCSCs phenotype by reducing the expression of YAP1 [60].

#### FOXM1

FOXM1 is considered to be an oncogenic protein complex that is involved in tumor angiogenesis, invasion and metastasis. Isovitexin could not only markedly reduce the sphere formation rate and colony formation rate of cultured LCSCs by preventing the overexpression of MnSOD and down-regulating the expression of FOXM1, but also inhibited the expression of CSCs markers in a dose-dependent manner. These results prove that isovitexin can restrain the stemness and tumorigenicity of LCSCs [61].

### TCM monomers up-regulate LCSCs-related tumor suppressor genes

Programmed cell death 4 (PDCD4) is a tumor suppressor gene that inhibits cancer cell proliferation and promotes apoptosis [62]. Isocorydine (ICD) is an alkaloid found in the traditional Chinese medicine Dactylicapnos scandens or Dicranostigma leptopodum, which can inhibit the proliferation of liver cancer cells lines and reduce the biomarkers and tumorigenicity of LCSCs [63]. ICD firstly time and dose dependently reduced the content of SP cells in vivo and vitro, decreased the expression of drug-resistant gene ABCG2, and inhibited cell growth by blocking the cell cycle. Then, it promoted the apoptosis of SP cells by activating the tumor suppressor gene PDCD4-associated apoptosis target [64].

## TCM Derivatives Inhibit LCSCs

### TCM derivatives regulate LCSCs-related signaling pathways

**Wnt/β-catenin signaling pathway:** Chrysin, as a natural flavonoid, is abundant in propolis and honey, and has been proved to have anti-proliferative effects on a variety of cancers comprising HCC [65]. 8-bromo-7-methoxychrysin (BrMC) is a synthetic analog of it, which has a stronger anti-tumor effect than chrysin, it plays an anti-HCC role by antagonizing Wnt/β-catenin signaling pathway. When treated with BrMC, the expression of β-catenin in LCSCs decreasd. Nevertheless, down-regulation of β-catenin expression could cooperate with BrMC to inhibit the tumor spherogenesis of LCSCs and the expression of CSCs markers CD133 and CD44 [66]. 6-C-(E-styrene)naringin (6-CEPN) is a new semi-natural derivative of naringenin produced by the reaction of naringenin with phenylacetaldehyde. 6-CEPN could significantly down-

regulate the levels of the direct targets SOX2, OCT4, NANOG, KLF4 and c-Myc transcription factors of Wnt/β-catenin pathway. And LCSCs were directly targeted by 6-CEPN through inducing β-catenin degradation and inhibiting its nuclear translocation [67].

**PI3K/AKT signaling pathway**

The activation of AKT downstream of PI3K/Akt/mTOR pathway is of great significance for the survival of CSCs. (Z)-3,5,4'-trimethoxystilbene (Z-TMS), a derivative of resveratrol, could inhibit the proliferation and division of DCLK1+ CSCs by blocking DCLK1 (CSCs marker) and promoted cell death. And after Z-TMS treatment, Akt phosphorylation in LCSCs was significantly inhibited [68]. WM130, a novel matrine derivative with better anti-tumor activity than matrine, reduced the expression of stemness-related genes EpCAM, CD133, CD90, OCT3/4, Sox2 and NANOG in a concentration-dependent manner to inhibit the self-renewal ability of LCSCs and the formation of hepatocellular spheres, up-regulated the expression of hepatocyte cytochromes P450, G-6-P, ALB and ALDOB to promote the differentiation of LCSCs into hepatocytes.and the above effects were achieved by inhibiting AKT/GSK3β/β-catenin signaling pathway [69]. Another novel matrine derivative, (6AS, 10S, 11AR, 11BR, 11CS)-10-methylamino-dodecahydro-3a,7a-diaza-benzo (de) (MASM), reduced the sphere formation ability of LCSCs and the expression of LCSCs markers via restraining the PI3K/Akt pathway and subsequent GSK3β activation, β-catenin phosphorylation and degradation. In addition, MASM promoted the expression of mature hepatocyte markers ALB, CYP1A3 and G-6-P, and ultimately inhibited self-renewal of LCSCs [70].

**STAT3 signaling pathway**

BrMC decreased sphere formation and self-renewal abilities of liver cancer stem cell-like cells (LCSLCs) in a dose-dependent manner, and down-regulated the expression of CSCs markers and the phosphorylation of STAT3. The synergistic effect of STAT3 inhibitor JSI-124 and BrMC demonstrated that BrMC reversed the stemness of LCSLCs by inhibiting STAT3 [71]. In a subsequent study, they found that the inhibitory effect of BrMC on LCSLCs dramatically reduced after heterotectomic expression of Twist1 [72]. All above shows that BrMC can inhibit the stemness of LCSLCs by inhibiting the STAT3/Twist signaling axis. Besides, it was found that SHP-1-mediated dephosphorylation of p-JAK2 and p-STAT3 played a vital role in the formation and invasion of tumors. Huang et al. prepared a new type of ZnAs@SiO2 nanoparticles with stronger anti-tumor effect and less side effects than ATO by reverse microemulsion method, which could up-regulate the expression of SHP-1 and down-regulate the expression of p-JAK2 and p-STAT3. It could also notably suppress the formation of tumor spheres and the expression of CSCs markers CD133, SOX-2 and Oct-4 in vitro by modulating the SHP-1/JAK2/STAT3 signaling pathway [73].

**TCM derivatives inhibit LCSCs-related EMT**

The chrysin derivative BrMC could inhibit the proliferation and self-renewal of CD133+ sphere cells and the expression of CD133 and CD44 markers of CSCs, down-regulate the expression of N-cadherin and Vimentin, and up-regulate the expression of E-cadherin and ZO-1 to suppress the invasion of LCSCs. And the EMT of LCSCs was suppressed by down-regulating the expression of Twist and β-catenin in LCSCs [74]. In addition, when BrMC combined with sorafenib, the expression level of EMT-related key protein Twist1 was reduced in a dose-dependent manner. The self-renewal, cell migration and invasion abilities of LCSCs remarkably diminished, and the cell apoptosis increased [75]. The 8-amino-ICD (d-ICD), a derivative of isocorydine, has stronger anticancer activity than ICD. In order to improve the anti-carcinogenic activity of d-ICD, Yan et al. designed and synthesized a new derivative named FICD, which could memorably inhibit the expression of Vementin, the main marker of EMT and target the CSCs of EMT transformation to initiate relapse with the combination of sorafenib [76].

**TCM derivatives inhibit LCSCs-related cytokines**

IL-6 is closely related to STAT3 and can promote tumor formation in many aspects. HGF is closely related to the growth, migration and morphogenesis of a variety of cells, and plays a key role in tumor invasion and metastasis. The combination therapy with BrMC and chrysin could effectively diminish the sphere formation of LCSCs as well as the expression of biomarkers CD133 and CD44, and also reduced the stemness of LCSCs by restraining the secretion of IL-6 and HGF [77].

**TCM derivatives inhibit the expression of LCSCs-related oncogenes**

As an oncogene, IGF2BP3 promotes the stemness-like cell phenotype of tumor cells as well as the migration and invasion potential of tumor cells [78]. d-ICD could suppress the expression of drug-resistant genes ABCB1 and ABCG2, as well as CD133, LGR5, IGF2BP3 and IGF2BP1. Besides, the over-expression of IGF2BP3 almost completely eliminated this effect, which proves that d-ICD targets LCSCs by inhibiting the expression of stemness genes through down-regulating IGF2BP3 [79].

## Discussion

LCSCs are considered to be the key to the growth, invasion, metastasis and recurrence of HCC, and one of the main reasons for the poor prognosis of HCC. As a traditional treatment method, TCM monomer extracts and derivatives (Table 1) could inhibit the stemness characteristics of LCSCs, such as proliferation, self-renewal, sphere formation, migration as well as invasion, and promote the apoptosis of LCSCs through a variety of ways, which included the regulation of the classical Wnt signaling pathway,

PI3-K/Akt signaling pathway, STAT3 signaling pathway and other eleven LCSCs-related signaling pathways (Figure 1), inhibition of the expression of EMT and related oncogenes in LCSCs. Among them, TCM monomers could also up-regulate miRNAs related to LCSCs and activate the expression of tumor suppressor genes, while TCM monomer derivatives could also inhibit the secretion of cytokines. Broadly speaking, TCM gives full play to the advantages of multi-target, multi-link and multi-level to target LCSCs.

| Category | Medicines |
|---|---|
| TCM monomers | Isocorydine、Ginsenoside Rh2、Casticin、Amarogentin、Curcumin、EGCG、Ovatodiolide、ψ-Bufarenogin、Baicalein、Docetaxel、Sophocarpine、Lupeol、Silibinin、2-Ethoxystypandrone、Cucurbitacin B、Glabridin、Catechol、Matrine、Pterostilbene、Isovitexin、Limonin、Wallichoside、GD extract、BJ fruit extract、EEDK、ATO |
| TCM derivatives | 4-methylumbelliferone、d-ICD、FICD、MAN-6DG、BrMC、6-CEPN、Z-TMS、WM130、MASM、ZnAs@$SiO_2$ nanoparticles |

**Table 1.** Traditional Chinese medicine monomers and derivatives against CSCs.

EGCG, Epigallocatechin gallate; GD, Gynura divaricata; BJ, Brucea javanica; EEDK, The ethanolextract of D. kaki leaves; ATO, Arsenictrioxide;d-ICD,8-amino-ICD;FICD,8-amino-isocorydinederivative;MAN-6DG,α-mangostin6-O-β-D-2-deoxyglucopyranosid; BrMC, 8-bromo-7-methoxychrysin; 6-CEPN, 6-C-(E-Phenylethenyl)Naringenin; Z-TMS, (Z)-3,5,4'-Trimethoxystilbene; WM130, matrine derivative,C30N4H40SO5F; MASM, (6aS, 10S, 11aR, 11bR, 11cS)-10-methylamino-dodecahydro-3a,7a-diaza-benzo (de).

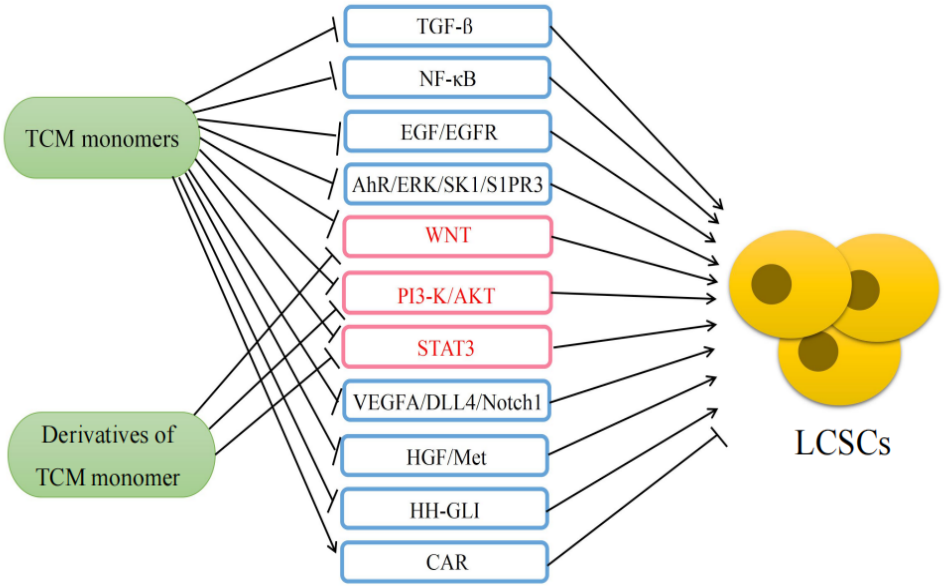


**Figure 1.** The signaling pathways targeted by Traditional Chinese medicine monomers and derivatives to inhibit liver cancer stem cells. Traditional Chinese medicine monomers and derivatives (green on the left), co-acting signaling pathways (red in the middle), other known signaling pathways (blue in the middle), and liver cancer stem cells (right), The positive effect is represented by ⟶, the negative effect is represented by ⊣

Although a large number of traditional Chinese medicine monomers and derivatives have been studied to inhibit LCSCs through various ways, there are still some compounds, such as including ginsenoside Rh2 (GRh2), Quercetin, 4-methylumbelliferone (4Mu), a coumarin derivative, and 6-O-β-D-2-deoxyglucopyranoside (MAN-6DG) which is a derivative of a natural xanthone named α-mangostin (α-MGT) in mangosteen pericarp, can inhibit the expression of LCSCs markers, self-renewal and differentiation, and reduce the number of LCSCs [80-83], but the specific mechanisms of their effects on LCSCs remain unclear. There is no doubt that further studies are needed to reveal the mechanisms of the effect of known TCM monomers and derivatives on LCSCs, and discover more TCM monomers

or TCM monomer derivatives that can inhibit LCSCs to provide more options for HCC and improve the prognosis and quality of life of patients by targeting LCSCs.

## Author Contributions

Z.-Y. Q. was responsible for literature search and writing the first draft. Y.-P. G. participated in literature search and provided writing advice. C.-C. B. and Y.Z. were responsible for drafting the writing ideas, guiding the writing of the article and finalizing the draft. All authors have read and agreed to the published version of the manuscript.

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