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Chinese herb in the treatment and regulation of cancer stem cells

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Abstract

Chinese Herb (CH) treatment, as one of the combination therapies for cancer, has the characteristics of multi-targets, multi-approaches and integrity. CH attenuates tumor angiogenesis, drug resistance, and immunomodulation by regulating cancer stem cell proliferation, which is the main mechanism to inhibit cancer progression. In this review, we discuss recent advance on the inhibition and regulation mechanism of Chinese Herb monomer, single drug extract and Chinese Herb compound on cancer stem cells, analyzed and considered the research status in order to provide ideas and references for the research of CH regulating cancer stem cells.

Introduction

Malignant tumor is seriously threatening human health, and the morbidity and mortality continue to increase. Although current therapies of cancer mainly include surgery, chemotherapy, radiotherapy, targeted therapy and immunotherapy, recurrence, metastasis and drug resistance after treatment of cancer remain a concern. With the continuous development of Stem Cell biology, an increasing number of studies hinting towards an effect of Cancer Stem cells (CSC) in tumor metastasis, -which maintain tumor growth through self-renewal, cause tumor recurrence and metastasis [1]. Chinese Herb treatment as an important methods of comprehensive treatment of malignant tumor, its multi-target, multi-pathway and integrity characteristics make its advantages in tumor treatment become more and more prominent. This paper will explore the intervention and regulation mechanism of Chinese Herb on cancer stem cells from three aspects: monomer of Chinese Herb, single drug extract and compound prescription of Chinese Herb, so as to provide references and ideas for the treatment of clinical malignant tumor with Chinese Herb.

Monomers of chinese herb: At present, there are many studies on natural compounds, and it has been proved that curcumin, resveratrol, and ginsenoside have anti-tumor effects. Meanwhile,more and more documents have found that natural compounds can also be used as treatment methods for CSC.

Curcumin: Curcumin, a plant polyphenol extracts from the Chinese Herb turmeric, is the most important active component of turmeric. Recent studies have shown that turmeric has some new pharmacological effects on top of its traditional effects, such as anti-inflammatory, scavenging oxygen free radicals, anti-viral, and anti-tumor effects. Studies have found that curcumin can regulate specific miRNAs in the dlk1-dio3 gene cluster to inhibit the proliferation and invasion of human prostate cancer CSC [1], cause the ceRNA effect [2], inhibit human prostate CSC, and reverse the activation of CSC characteristics caused by tobacco smoke [3]. Curcumin not only inhibits the expression of CSC by inhibiting the Sonic Hedgehog pathway [4-5], the aromatic hydrocarbon receptor ERK/SK1/S1P3 signaling pathway [6] and the JAK2/STAT3 signaling pathway [7], but also restrains the migration of breast CSC by affecting E-cadherin /beta-catenin [8-9]. At the same time, the researchers [10] found that curcumin can enhance the ability of mitomycin C to induce the death of breast cancer CSC and inhibit the self-renewal ability of CSC, and the combination therapy with EGCG can reduce the CD44 positive cell population, specifically inhibit the phosphorylation of STAT3 [11], and induce mesenchymal epithelial transformation (MET), thus making CSC more sensitive to 5-fu [12]. Therefore, the regulation of CSC is one of the important anti-tumor mechanisms of curcumin.

Resveratrol: Resveratrol (RES) is a kind of bioactive natural polyphenols extracted from polygonum cuspidatum, grape, mulberry and other plants, also known as Stilbenol, which is a chemical preventive agent for tumors. As a natural tumor chemoprophylaxis, RES has good anti-tumor activity in the three stages of tumor genesis, promotion and expansion, and can inhibit tumor cells in each stage. Recent studies have found that RES can activate the autophagy activity of glioma stem cells, increase their radiosensitivity, inhibit proliferation and promote

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apoptosis [13], and also activate p53 to inhibit the expression of glioma stem cell Nanog and induce the differentiation of glioma stem cells [14]. In breast cancer CSC, RES can block the Wnt/β-catenin signaling pathway to inhibit breast CSC and induce autophagy [15], increasing Argonaute2 activity and leading to an increase in the expression of anti-cancer miRNAs [16]. RES inhibits the proliferation of colorectal cancer CSC, promotes apoptosis, upregulates the expression of MICA/B in colorectal cancer CSC, enhances cellular immunogenicity [17], activates p53 to induce miR-145 and miR-200c to inhibit the Stem cell characteristics and epithelial mesenchymal transformation of CSC [18]. In addition, RES can inhibit pancreatic cancer stem cell characteristics of human and Kra transgenic mice by inhibiting pluripotent maintenance factors and EMT [19], inhibit proliferation and tumorigenicity of myeloblastoma CSC, and enhance their radiosensitivity [20].

Honokiol: Honokiol (HNK), the extract of dried bark, root bark and branch bark of Magnolia officinalis, has anticancer effect in many kinds of cancer cells. HNK can reduce the expression of non-adherent mammospheres, pluripotent factors and aldehyde dehydrogenase activity to increase the expression of hepatic kinase B1 (LKB1), inhibit individual cell movement, and eliminate the stem-cell like phenotype of breast cancer cells [21]. In glioblastoma multiforme 8401 (GBM8401), HNK inhibited the proliferation of parental cells and cancer stem cell like population (SP) cells in a dose-dependent manner, significantly enhancing the ability of the MGMT inhibitor o6-benzyl guanine (o6-BG) to reduce SP resistance to timozolid [22]. At the same time, HNK can target melanoma stem cells by inhibiting Notch-2 signaling, thus effectively inhibiting melanoma cells [23], reversing EMT and partially inhibiting CSC characteristics through miR-141/ZEB2 axis [24], inducing cell apoptosis, inhibiting Wnt/β-catenin conduction and inhibiting epithelial-mesenchymal transformation to eliminate oral CSC [25]. HNK, as a HIF inhibitor, plays an important role in inhibiting hypoxia-inducible factor (HIF) pathway in the treatment of human gioblastoma, blocking the expression of CSC markers [26].

Ginsenoside: Ginsenoside is a kind of sterol compound, which mainly exists in medicinal materials of the genus ginseng. Its main anti-tumor active ingredients include Rh1, Rh2, Rh3, Rb1, F2, Rg3, Rg5, etc. It has strong anti-cancer effect on breast cancer, cervical cancer, colorectal cancer, esophageal cancer, pancreatic cancer, etc. Studies have found that ginsenoside Rb1 and compound K have a strong cytotoxic effect on CSC, which can inhibit the self-renewal of CSC and increase the sensitivity of CSC to chemotherapy drugs, mainly by down-regulating the expression of β-catenin/TCF dependent transcription and its target genes ABCG2 and P-glycoprotein [27]. Ginsenosides Rh2 can reduce the number of Lgr5-positive CSC to inhibit the growth of human skin squamous cell carcinoma [28], down-regulate the expression of IL-6, inhibit the proliferation and promote apoptosis of CSC of nasopharyngeal carcinoma in vitro [29]. Ginsenoside F2 can induce the apoptosis of CSC by activating endogenous apoptosis pathway and mitochondrial dysfunction, and ginsenoside F2 can initiate the autophagy process of CSC [30]. In colorectal cancer, 20 (S) -ginsenoside Rg3 inhibited the proliferation of CSC in colorectal cancer, and induced the apoptosis of CSC in colorectal cancer by caspase-3 and caspase-9 pathways [31]. Ginsenoside, as a representative drug of Fuzheng Chinese Herb, its inhibitory effect on CSC is an important embodiment of its Fuzheng anti-cancer effect, which needs to be further studied.

Arsenic Trioxide: Arsenic trioxide (ATO), commonly known as arsenic, is an ancient mineral Chinese Herb with strong toxicity and has made an important contribution to the treatment of promyelocytic leukemia. With the development of anti-tumor research, arsenide has shown a unique therapeutic effect on lung cancer, pancreatic cancer, glioblastoma, liver cancer and other cancers. It has been found that ATO can inhibit the proliferation of lung cancer CSC and reduce its colony formation ability by reducing the expression of Gli1 and its downstream genes such as N-myc and GAS1 [32], and inhibit the activity of pancreatic cancer CSC in vitro and in vivo by binding to SHH-Gli protein [33]. In glioblastoma, ATO down-regulates the Notch pathway to reduce the proliferation and recurrence of glioblastoma [34], and low ATO concentration leads to the morphological differentiation of glioblastoma stem cell-like cells [35]. At the same time, ATO and parthenolide synergistically inhibit the proliferation and induce apoptosis of hepatoma HepG2 cells, effectively inhibit hepatoma stem cells [36], and block the cell cycle by down-regulating the expression of sorting positive cells, thereby inhibiting cell proliferation and promoting cell apoptosis and necrosis to exert anti-tumor effect [37].

Bufalin: Bufalin is a monomer compound extracted from toad venom. It is a polyhydroxyl steroid and is one of the effective components of anti-tumor drug cinobufagin. It can inhibit tumor cell proliferation, induce tumor cell autophagy and reverse tumor drug resistance. It can selectively inhibit a variety of tumors in vitro and in vivo. It has been found that bufalin can inhibit gemcitabine resistant pancreatic cancer CSC and block the activation of Hedgehog signaling pathway [38]. In inhibiting the stemness of C1OS-CSC, the stemness of osteosarcoma cells is controlled mainly through the regulation of DNMT1 and p27 by miR-148A [39]. Some researchers have also found that bufalin can induce the apoptosis of CSC by up-regulating the expression of caspase3 and PARP and down-regulating the expression of human telomerase reverse transcriptase, and enhance the inhibitory effect of temozolomide on CSC by activating the mitochondrial apoptosis pathway [40].

Tanshinone IIA: Tanshinone IIA (Tan-IIA) is a diterpenoid quinone ingredient extracted from the Chinese Herb salvia miltiorrhiza, which has neuroprotective, anti-inflammatory, anti-tumor and other biological activities. Its anti-tumor activities mainly include promoting tumor cell apoptosis, reversing tumor multi-drug resistance, inhibiting angiogenesis and metastasis. Tan-IIA can targets and inhibits CSC, and through the block IL - 6/STAT3/NF-kB signaling pathways in inhibiting the growth of human breast CSC in vivo and in vitro [41], also can through the pathway inhibition of proliferation, less stemness and induction of apoptosis and targeted and inhibit the CSC [42], high dose of Tan-IIA can promote apoptosis of PG stem cell-like cells, its ability to promote apoptosis, Its pro-apoptotic capacity is equal to or greater than that of cisplatin[43] .After Tan-IIA treatment, the adhesion, invasion and chemotaxis ability of gastric cancer MKN-45 cells were significantly inhibited, the heterogeneous adhesion molecule CD44V6 was decreased, the expression of E-acdherin was up-regulated, and the ability of tumor cells to penetrate the extracellular matrix and basement membrane was decreased [44]. Tan-IIA can also inhibit the migration and invasion of cervical cancer stem cell-like cells by inhibiting the transcriptional activity of YAP [45].

Emodine: Emodine is the active component of rhubarb root and rhizome, which has anti-tumor and other biological activities. Emodine inhibits mouse solid sarcoma S-180, mouse liver cancer, breast cancer, lymphosarcoma, melanoma, lung cancer A-549.It has been found that emodine can significantly inhibit the stemness signals such as Notch-1, β-catenin pathway and STAT3 of GSC, thus blocking the self-renewal of GSC [46]. And through ROS-related mechanisms and inhibition of ABCG2 function, it can effectively reduce the ratio of CSC-like SP cells and inhibit colony formation [47]. Emodine combined with AZT synergistically inhibited the proliferation of leukemia CSC by down-

regulating the expression of BCL-2, NF-κB, and TGF-β [48], and promoted the expression of tyrosine phosphatase SHP-1 and inhibited STAT3 activation by inhibiting c-Src, JAK1/2 kinase [49].

Single drug extract: Some Chinese herb extracts (alcohol extracts or water extracts, etc.) have also been shown to have an effect on CSC functions such as differentiation, apoptosis, drug resistance, which can provide new ideas for the treatment of CSC.

Sculellaria barbata: Sculellaria barbata is a perennial herb of the genus scutellaria in the labiaceae family, which has the functions of clearing heat and detoxifying, promoting blood circulation and removing stasis, relieving swelling and pain, etc. The anticancer effect of Sculellaria barbata is relatively obvious, and it is a commonly used drug in clinical tumor treatment. Its anti-tumor mechanism mainly focuses on inducing apoptosis of tumor cells and promoting autophagy of tumor cells. Scutellaria barbata has obvious inhibitory effects on colorectal cancer CSC, can inhibit Hedgehog signaling pathway, down-regulate the levels of colon cancer CSC markers CD133 and Lgr5 mRNA, reduce colon cancer CSC Hedgehog signaling pathway Ptch1 and Gli mRNA transcription, and inhibit colon cancer CSC Self-renewal [50] can also inhibit the growth of colorectal cancer CSC, enhance cell β-catenin protein phosphorylation, and degrade β-catenin expression [51].

Scutellaria baicalensis: Scutellaria baicalensis is the dried root of Scutellaria baicalensis, a herb of the family labiaceae, which has the functions of clearing heat, drying dampness, reducing fire and detoxification. Modern pharmacological studies have shown that Scutellaria baicalensis has anti-oxidant, immunomodulatory and anti-tumor effects. Scutellaria baicalensis extract and its main active flavonoids can target SP cells by regulating the expression of ABCG2 protein [52], and induce high expression of HSP70 in mouse liver cancer H22 cells, which can increase the mice's ability to treat allograft tumors active immunity [53].

Celastrus orbiculatus: Celastrus orbiculatus is a plant of the genus Cornelius, which has the functions of removing wind, dehumidifying, activating blood and detoxifying. Modern pharmacological studies showed that the plant had anti-tumor, anti-inflammation, anti-virus and anti-oxidation activities. The extract can inhibit the invasion and metastasis of stem-like cells of esophageal squamous cell carcinoma, regulate the generation of mitochondria mediated by DJ-1 [54], and reverse the epithelial mesenchymal transformation of liver cancer cells, whose molecular mechanism may be related to the mTOR signaling pathway [55].

Oldenlandia diffusa: Oldenlandia diffusa is the whole plant of the genus Oldenlandia of the rubiaceae family. It has the functions of clearing heat and detoxifying and benefiting dampness and drenching. More and more modern pharmacological studies have shown that it has significant anti-tumor effect. Oldenlandia diffusa significantly inhibits the expression of CSC markers LGR-5 and OCT-4 in vitro and in vivo, and inhibits the growth of CSC in colorectal cancer, while inhibiting the activation of Wnt/β-catenin signaling pathway and regulating the expression of key factors is its key Mechanism [56].The ethanol extract of the plant can significantly reduce the mRNA levels of PCNA, Lgr5, β-catenin, c-myc and survivin in a dose-dependent manner, and inhibit the proliferation of CSC in Colorectal cancer [57]. Shi yurong [58] found that colonic CSC differentiation could be inhibited by restaining the activity of Wnt signaling pathway.

Ligusticum wallichii: Ligusticum wallichii is the dried rhizome of Umbelliferae chuanxiong, which has the functions of promoting blood circulation and promoting qi, removing wind and relieving pain. Modern pharmacological studies have shown that Ligusticum chuanxiong has a good therapeutic effect on cardiovascular and cerebrovascular diseases, nervous system diseases, tumors and so on.Studies have shown that Ligusticum wallichii can inhibit the expression of VEGF, HIF-1α and EMT-related proteins in stem-like cells [59]. It can also inhibit the primary tumor model and recurrence model of lung cancer stem cell-like tumor-bearing mice, and its mechanism is related to the inhibition of HIF-1α and EMT-related molecule expression [60]. Further studies also confirmed that Ligusticum wallichii could improve the hypoxic microenvironment of tumor [61] by inhibiting HIF-1α expression [62], which had a inhibit ing effect on CSC. Ligusticum wallichii may also inhibit CSC by inhibiting the mRNA expression of EMT-related marker proteins at the mRNA level [63].

other drugs: In addition, some Chinese Herbs have anti-tumor effects. The application of Sophora flavescens extract to CSC has been found to inhibit the proliferation of CSC and induce the apoptosis of CSC in vitro, as well as inhibit the activity of Wnt pathway [64]. Purslane extract can significantly inhibit the proliferation of CSC in vitro by inducing apoptosis and influencing cell cycle [65]. Yam extract can inhibit the proliferation rate of colon cancer H29 cells and reduce the proportion of CSC [66]. Realgar can effectively induce LCSC apoptosis by affecting caspase-dependent mitochondria [67].

Chinese Herb Compound: Chinese Herb Compound have a long history in cancer treatment, and they have shown advantages in prolonging the survival period and improving the quality of life of patients. Therefore, more and more cancer patients are seeking Chinese herb medicine treatment. Chinese herb medicine treatment is also considered to be one of the adjuvant therapies for cancer. With the discovery of research, there are more and more studies on the regulation of CSC and tumor progression by Chinese Herb Compound, which can better reflect its multi-target and multi-pathway effect.

Sijunzi decotion: Sijunzi decotion, originated from "taiping huimin he ji jufang", is composed of ginseng, atractylus atractylus, poria coxa and liquorice, and has the effect of invigorating the spleen and stomach. Studies have shown that sijunzi decoction can effectively inhibit proliferation and promote apoptosis of SP cells with CSC characteristics [68], inhibit tumorigenesis of gastric cancer SGC-7901SP cells, and promote apoptosis of tumor cells [69]. Sijunzi decoction serum can up-regulate Bax, down-regulate Bcl-2, promote the release of Cytochrome C, activate the Caspase-3-mediated apoptosis pathway, and inhibit the growth of SP cells in thyroid cancer cells [70].

Pien Tze Huang: Pien Tze Huang, originated from the Ming Dynasty, has a history of more than 400 years. It consists of bezoar, panax notoginseng, snake gall, musk and other drugs. It has the effects of clearing heat and detoxifying, cooling blood and removing blood stasis. Studies have found that Pien Tze Huang can reduce the number of stem cells in HT-29 and SW620 colorectal cancer cell lines and inhibit the proliferation of colorectal cancer cells in these two cell lines [71], and can also significantly reduce the proportion of colorectal cancer stem cell-like SP cells in a dose-dependent manner. Reduce the viability and spheroid formation ability of HT-29 SP cells, and regulate the related biological behavior of CSC [72]. At the same time, Pien Tze Huang can significantly inhibit the growth and tumorigenicity of hepatocellular carcinoma stem cells, possibly by regulating cell proliferation, the ratio of apoptosis-related proteins Bcl-2 / Bax, CDK4, CyclinD1 and miR-483-5p and the expression of their target gene CDKN1A (p21). Thereby inhibiting liver cancer stem cell growth and inducing apoptosis [73].

Yiqijiedu Formulae: YiqiJiedu Formulae is a Chinese Herb compound consisting of zedoary turmeric, Radix paeoniae alba,

and Atractylodes macrocephala, and more and more modern pharmacological studies suggest that it has an important role in autophagy and inducing apoptosis of tumor cells. Yiqi Jiedu Formulae can reduce the proliferation rate of ACHN renal cancer CSC, increase the expression of P53 protein, and increase the apoptosis rate [74]. It can significantly inhibit the proliferation of CNE2 stem cells in nasopharyngeal carcinoma and can affect the CSC marker CD44 and ABCG2 expression activityin CNE2 cells, promote CSC apoptosis [75], up-regulate the expression of miR-200b to inhibit CSC, thereby inhibiting the growth and proliferation rate and invasion potential of nasopharyngeal carcinoma [76].

Yiqibushen Formula: Yiqibushen Formula is a Chinese Herb compound composed of spatholobus, astragalus, cistanche, fructus psoraleae, herba epimedium, etc. Related studies have shown that it has the function of immune regulation, promoting the effect of anti-hypoxia and anti-tumor. It has been found that Yiqibushen Formula may down-regulate the expression of CSC surface markers in gastric cancer by regulating CSC niche and Notch signal pathways, induce the benign differentiation of gastric cancer CSC, and achieve a significant anti-proliferation and metastasis effect on gastric cancer cells [77]. By down-regulating the expression of CSC surface markers CD24, CD44, Ep CAM, reducing the proportion of CSC surface markers in tumor, inducing gastric cancer CSC benign differentiation and inhibiting gastric cancer cell proliferation and metastasis [78].

Xiaotan Sanjie Formula: Xiaotan Sanjie Formula is a Chinese Herb compound consisting of Pinellia, Nanxing, Ji Nei Jin, Chen Pei, etc., which is an empirical formula of "treatment from phlegm". Studies have found that Xiaotan Sanjie Formula may down-regulate the expression of Notch-1 and Hes1 genes, reduce tumor angiogenesis and inhibit the proliferation of gastric cancer stem cells in a dose-dependent manner [79], enhance the expression of apoptotic protein Bax, inhibit of apoptotic protein Bcl-2 expression decreased,and dose-dependent induce the apoptosis of colon cancer stem cell-like cells [80]. By reducing the expression of PCNA in gastric cancer cells, Xiaotan Sanjie Formula can inhibit the proliferation activity of gastric cancer cells, and reduce the heterogeneous adhesion by affecting the expression of adhesion molecules CD44 and CEA of gastric cancer cells [81].

Conclusion

In recent years, increasing numbers of patients have been attracted to use CH as an adjuvant therapy option for cancers. Numerous studies have confirmed that CH in combination with chemoradiotherapy is capable of promoting the efficacy of and diminishing the side-reaction induced by chemotherapy and radiotherapy. Because the mechanism of CSC promoting tumors is complex, comprehensive treatment methods are particularly important. Chinese Herb exerts multi-target and multi-pathway effects, and has advantages in inhibiting the function of CSC. As mentioned above, enriched natural extracts and traditional Chinese medicine formulae able to interfere with drug resistance and self-renewal pathways in CSCs have been identified.

However, studies on the effects of Chinese Herb in CSC are limited to the observation of the proliferation, apoptosis and differentiation of CSC cells, but the detailed mechanism of action is few and awaiting in-depth study, and there is no in-depth study on the detailed mechanism of action. Meanwhile, CSC lacks clear detection markers, and different CSC also lack specific markers, which causes a lot of trouble for the intervention and regulation of CSC by Chinese Herb. However, this limitation is a common limitation of traditional Chinese medicine and western medicine, and it is also an opportunity for traditional Chinese medicine to play a multi-target role in regulating CSC. In this review, we illustrated the mechanism of antitumor activity of CH components by regulating the biological function of CSC. However, in order to apply the potential multi-target activity of CH to cancer therapy and expand the biomedical applications, we must provide a deeper insight and substantial understanding to the CH effective components and the mechanism of CH regulating CSC.

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Competing interests

The authors declare that they have no competing interests.

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