Review Article

Targeting cancer stem cells and signaling pathways by resveratrol and pterostilbene

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Abstract

In past decades, increasing evidence regarding cancer stem cells (CSCs) may account for carcinogenesis, tumor drug-resistant, and metastasis. CSCs are even considered as the root causes of tumor recurrence and metastases. Targeting CSCs may provide a new clue to cure cancer. Epidemiological and clinical studies have suggested that intake of dietary natural products may bring health benefits including lowering risk of cancer incidence. In this review, we have particularly focused on targeting signaling pathways of CSCs by natural resveratrol and its dimethylated derivative pterostilbene. © 2017 BioFactors, 44(1):61–68, 2018

Keywords: *resveratrol; ptereostilbene; stem cells; cancer; signaling pathways*

1. Introduction

Cancer is becoming a major public concern because it is among the leading causes of death in the world. According to a recent statistic from the American Cancer Society, an estimated 1.69 million of new cases of cancer will be diagnosed, and more than 600 thousands of people will die from the disease in 2017 [1].There are various types of cancer treatments, including surgery, chemotherapy, radiation therapy, immunotherapy, hormone therapy, targeted therapy, and stem cell transplantation. Patients suffering from cancer receive different types of treatment, depending on the type and the stage of cancer. Although current strategies for cancer treatment are developed, serious treatment-related side effects, treatment resistance, and relapse lead to cancer's high mortality.

In cancer biology, cancer cells display extremely intricate hallmarks, including genetic instability, tenaciously proliferative capacities, cell death resistance, replicative immortality, angiogenesis, invasion, and metastasis [2]. Of note, the concept of cancer stem cells (CSCs) is suggested by recent studies. CSCs represent a small group of cells rooted in tumors to preserve stemness and regrow the entire cancer. Although many issues regarding how the CSCs work remain unknown, the existence of CSCs has important implications for treatment resistance and tumor relapse [3,4]. Hence, targeting CSCs may be a promising strategy for improved cancer treatment.

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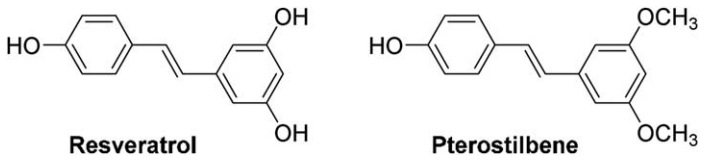

FIG 1 *Chemical structures of resveratrol and pterostilbene.*

In recent decades, increasing epidemiological and clinical studies have suggested that intake of dietary natural products may have health benefits, including lowering the risk of cancer incidence and relapse [5,6]. Numerous phytochemicals have been demonstrated to counteract multiple oncogenic targets involved in cancer growth, invasion, and metastasis. Moreover, certain phytochemicals have been identified as targets of CSC stemness [7]. Therefore, natural products and their derivatives provide almost one-third of all novel anticancer drugs approved by United States Food and Drug Administration (US FDA) [8]. In this review, we particularly focus on targeting signaling pathways of CSCs by natural phenol resveratrol and its dimethylated derivative pterostilbene.

1.1. A brief introduction of CSCs

Cancer stem or tumor-initiating cells are a small group of cancer seed cells within the tumor. This theory proposes that CSCs not only possess the exclusive ability to regenerate the neoplasm but also have similar properties to normal stem cells, that is, self-renewal and differentiation. The earliest experimental case regarding CSCs was provided by John Dick and his colleagues [9]. These researchers first identified the hierarchy of human acute myeloid leukemia cells. Only the leukemia cells with the normal human hematopoietic stem cell markers CD34 + CD38– were the leukemia-initiating cells, as they were able to propagate leukemia in mice. Along with this discovery, researchers observed a panel of CSCs in a wide variety of cancers, such as breast, colon, lung, and brain.

Increasing evidence supported that epigenetic mechanisms play a key role in the formation and function of CSCs, as well as tumor heterogeneity, tumorigenicity, tumor progression, and metastasis [4]. The interaction between epigenetic incidents and the microenvironment where the tumor survives regulates the plasticity of CSCs and shapes tumor architecture [10]. In particular, this interaction gives rise to altered signaling pathways in CSCs communication and may result in the development of novel anti-CSC agents. Hence, the classic signaling pathways linked with CSCs, that is, Bmi-1, Shh, and Wnt/β-catenin pathways, have come to the forefront of current drug targets. These small- and macromolecular candidates [11] include kinase inhibitors, polypeptides, and compounds from natural plants [12].

1.2. Chemical aspects of natural phenol resveratrol and pterostillbene

Recent studies have demonstrated that plant-based foods have health promoting effects such as antioxidants and cancer prevention [13]. Hence, increasing attention has been given to separating nutritive and non-nutritive ingredients from vegetables and fruits that play potential roles in chemoprevention. Resveratrol (Fig. 1) is a highly bioactive natural polyphenolic substance that was first found in the root of white hellebore (*Veratrum grandiflorum*) in 1940 [14]. Natural resveratrol, which exists in grapes, berries, peanuts, mulberry and other plant-based foods, has a significant treatment effect on leukemia, breast cancer, head and neck cancer, thyroid cancer, and other tumor types. Additionally, resveratrol can inhibit the three stages of cancer: initiation, promotion, and development. Figure 1 illustrates the chemical structures of resveratrol and pterostilbene.

Pterostilbene is a derivative of resveratrol with 3,5-dihydroxyl groups replaced by two methoxyl groups. Pterostilbene mainly exists in grapes, blueberries, tomatoes, and other berries. It may be a more effective antioxidant and anti-cancer molecule because its two unique methoxyl groups confer a higher permeability and oral absorption rate. Additionally, the half-life of pterostilbene is seven times longer than that of resveratrol. Recent studies consider pterostilbene as the "next generation of resveratrol", in which it will play a significant role in chemoprevention and treatment of human diseases [15,16].

2. Resveratrol and pterostilbene target CSCs

It is widely accepted that dietary habits have a powerful influence on cancer risks [17]. For example, traditional Mediterranean diets rich in natural plants can lower the risk for many types of cancers. The protective ingredient resveratrol in the Mediterranean diet has been identified as a broad-spectrum preventative agent against cancer, as well as aging, diabetes, and cardiovascular diseases. Researchers have recently discovered that resveratrol and its analogue pterostilbene target CSCs via multiple signaling pathways (Table 1)

2.1. Breast cancer stem-like cells

Breast cancer is the most common malignant tumor in females worldwide. The incidence of breast cancer is greater in developed countries than in developing countries. Beyond genetic factors, the main risks are due to lifestyle including but not limited to unhealthy dietary fats, obesity, and lack of physical activities. Despite improved diagnostic and treatment strategies, the 5-year survive rate of advanced breast cancer is still unsatisfactory. Recent studies suggest that breast CSCs are responsible for therapy-resistance and metastasis. Therefore, removal of breast CSCs might represent the most promising approach to breast cancer therapy.

Studies in recent years elucidated that resveratrol inhibits breast CSCs behavior [36,37]. For example, Fu et al. demonstrated that resveratrol significantly suppressed the proliferation of breast CSCs and lowered the size and number of mammospheres. NOD/SCID (nonobese diabetic/severe combined

TABLE 1 ***CSCs signaling pathways associated with resveratrol and pterostilbene***

Compound	*Dosage (μM)*	*CSC*	*Results*	*Refs*
Resveratrol	40	Breast CSCs	↓ Proliferation, ↓ Percentage of breast CSCs population,	[18]
			↓ Size and number of mammospheres, ↓ Tumor xenograft growth, ↓ Tumor breast CSCs population in NOD/SCID mice, ↑ autophagy, ↑ LC3-II, ↑ Beclin-1, ↑ Atg-7 in CSCs, ↓ Wnt/β-catenin signaling.	
Resveratrol	100	Breast CSCs	↓ cell viability, ↓ mammosphere formation, ↑ apoptosis, ↓ lipid synthesis, ↓ FAS, proapoptotic genes (DAPK2 and BNIP3), ↓ proliferation,	[19]
Resveratrol	50	Breast CSCs	↑ expression and activity of Ago2 ↑ expression of a number of tumor- suppressive microRNAs(miR-16, 141, 143, −200c).	[20]
Resveratrol analog HS-1793	2.5	Breast CSCs	↓ hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor protein (VEGF) under hypoxic conditions, ↑ ionizing radiation-induced apoptosis in hypoxic FM3A cells.	[21]
Pterostilbene	25	Breast CSCs	↓ mammosphere formation, ↓ mammosphere number, ↑ phosphorylation of β-catenin, ↓ hedgehog protein expression, ↓ Phosphorylation of Akt and GSK3β, ↓ c-Myc, ↓ cyclin D1, ↓ CD44.	[7]
Pterostilbene	10	Breast CSCs	↑ E-cadherin, ↓ NF-κB, ↓ EMT-associated molecules (Twist1,vimentin), ↓ CSCs number, ↓ invasiveness, ↑ miR488.	[22]
Resveratrol	200	Leukemia	↓ proliferation, ↑ growth-inhibition effect on peripheral blood mononuclear cells (PBMCs),	[23]
		CSCs		
			↑ CIKs-mediated cytolysis, ↑ expression of NKG2D ligands and DR4, expression of DcR1	
Resveratrol	50	Leukemia	↓ proliferation, ↓ CSC-related Shh expression, ↓ Gli-1 nuclear translocation, ↓ cell viability in IL-6-treated HL-60 cells.	[24]
		CSCs		
Resveratrol -GSE	Resveratrol:9/ GSE:12.5 μg/ml	Colon CSCs	↓ the number of crypts containing cells with nuclear β-catenin, ↑ Apoptosis, ↓ proliferation, ↓ sphere formation, ↓ nuclear translocation of β-catenin, ↓ protein levels of Wnt/β-catenin pathway, ↓ c-Myc and cyclin D1.	[12]
			↑ mitochondrial-mediated apoptosis, ↑ p53, ↑ Bax/Bcl-2 ratio.	
Resveratrol	300	Glioma CSCs	↓ Proliferation, ↑ necrosis.	[25]
Resveratrol	75	Glioma CSCs	↓ Proliferation, ↑ radio sensitivity,	[26]

TABLE 1 *(Continued)*

Compound	Dosage (μM)	CSC	Results	Refs
			↓neural stem cell marker CD133, ↓ self-renewal, ↑ autophagy, ↑ apoptosis ↑ DNA repair.	
Resveratrol	100	Glioma CSCs	↓Proliferation, ↑ cell mortality, ↓cell motility, ↓ EMT	[27]
Pterostilbene	1 or 2 mg/kg	Glioma CSCs	↑ miR-205, ↓ GRP78, ↓ β-catenin, ↓ Notch, ↓ irradiation resistance, ↓ tumorigenesis.	[28]
Resveratrol	100	Head and neck CSCs	↓ self-renewal property, ↓ stemness genes signatures (Oct 4, Nanog, and Nestin), ↓ EMT markers (Slug, ZEB1, N-cadherin, E-cadherin, and Vimentin).	[29]
Resveratrol	50	Thyroid CSCs	↓ Stem cell markers (NANOG, OCT4,SOX2), Aldefluor, ↓ proliferation, ↓ invasiveness, ↑ apoptosis, ↑ differentiation.	[30]
Resveratrol	50	Ovarian CSCs	↑ apoptosis, ↑ cell death, ↓ self-renewal, ↓ stem cell markers(NANOG,SOX2).	[31]
Resveratrol	50	Nasophary-ngea carcinoma CSCs	↓ CSC properties, ↓ p53, ↓ stemness, ↓ EMT, ↓ miR-145, ↓ miR-200	[32]
Resveratrol	15	MelanomaCSCs	↓ α-MSHsignaling-related molecules, (β-catenin, c-Kit, and MITF), ↓ Nuclear translocation of MITF, ↓ viability, ↓ invasiveness, ↓ stem cell characteristics.	[33]
Pterostilbene	20	HepatomaCSCs	↓ stem cell number, ↓ sphere formation, ↓ stemness gene(CD133,c-Myc), ↓ COX-2, ↓ invasion and migration, ↑ apoptosis.	[34]
Pterostilbene	20	Lung CSCs	↓ self-renewal, ↓ MUC1, ↓ NF-κB, ↓ CD133, ↓ β-catenin, ↓ Sox2.	[35]

immunodeficient, abbreviations in Table 2) mice that received injected resveratrol (100 mg/kg/d) displayed significantly reduced xenograft size and a decreased breast CSC subpopulation in tumors. In addition, the indicators of autophagy, LC3-II, Beclin-1, and Atg-7, were well-promoted by resveratrol in the breast CSCs via the Wnt/*β*-catenin signaling pathway. Pandey et al. noticed that resveratrol lowered lipogenesis and modulated viability, mammosphere formation, and apoptosis in breast CSCs. The molecular basis of resveratrol action in breast CSCs involves the down-regulation of the fatty acid synthase (FAS) gene coupled with the upregulation of proapoptotic genes, such as DAPK2 and BNIP3. In mice, resveratrol functioned similarly and showed almost no toxicity.

MicroRNAs are small noncoding RNAs that provide fine-tuned regulation of multiple target genes. In fact, growing evidence indicates that microRNAs are potential therapeutic targets regarding the pathogenesis of a variety of diseases [38]. Similar to the stilbene derivatives, pterostilbene and resveratrol impair breast CSCs properties. Hagiwara et al. reported that both pterostilbene and resveratrol effects on breast CSCs may involve microRNAs [20]. Breast CSCs treated by resveratrol or pterostilbene showed improved activity of Argonaute2, a key regulator for microRNAs processing, and led to increased expression of tumor-suppressive miRNAs that inhibited the growth of breast CSCs. Mak et al. identified that pterostilbene impaired M2-tumor-associated macrophage-induced proliferation and metastatic capacity (epithelial-mesenchymal transition, EMT) of breast CSCs by modulating the NF-*κ*B/microRNA 448 circuit [22].

In addition to microRNAs, pterostilbene also affects breast CSCs. Breast CSCs exposed to pterostilbene showed reduced expression of the stem cell marker CD44 and stemness activity. This reduction occurs because pterostilbene augments *β*-catenin phosphorylation through blunting the hedgehog/Akt/

TABLE 2 *Abbreviations*

Full name	*Abbrev.*	*Full name*	*Abbrev.*
CSCs	CSCs	Anaplastic thyroid cancer	ATC
Non-obese diabetic/severe combined immune-deficient	NOD/SCID	M2-polarized tumor-associated macrophage	M2-TAM
Epithelial-mesenchymal transition	EMT	Stage-specific embryonic antigen 1	SSEA1
DR4	DR4	Aldehyde dehydrogenase	ALDH
DcR1	DcR1	Reactive oxygen species	ROS
IL-6	IL-6	Melanocyte hormone	α-MSH
Shh	Shh	Lung CSCs	LCSCs
Chronic myeloid leukemia	CML	GBM	GBM
LSCs	LSCs		

GSK-3β signaling pathway, thereby reducing the expression of its cascade proteins c-Myc and cyclin D1 and decreasing breast CSC stemness [39]. Moreover, another resveratrol analogue 4-(6-hydroxy-2-naphthyl)-1,3-benzenediol (HS-1793) was reported to counteract the hypoxic tumor environment to enhance the radio sensitivity of breast cancer cells by targeting HIF-1α and VEGF proteins [21].

2.2. Leukemia stem cells

Relapse is the major obstacle for patients with leukemia. LSCs are suggested to be relapse-relevant subpopulations in the leukemic hierarchy because of their self-renewal and dormancy features [40]. Eradicating LSCs may lead to a cure for leukemia.

In the acute myeloid leukemia stem-like cell line KG-1a, which harbors $CD34^+CD38^-$ markers on the cell surface, Peng et al. showed that resveratrol suppressed the phosphorylation of PLKB1 resulting in cell senescence and apoptosis [23]. Likewise, resveratrol was shown to sensitize drug resistant KG-1a cells to drug treatment and immune evasion [24]. In addition to suppressing half of the KG-1a cell growth, resveratrol was found to sensitize LSCs to cytokine-induced CD3 + CD56+ natural killer cell-like T lymphocytes. In regard to mechanism, resveratrol enhanced cell-surface expression of NKG2D ligand and death receptor 4 (DR4) but inhibited the expression of decoy receptor 1 (DcR1) in stem cell-like KG-1a cells.

An additional mechanism linked to the resveratrol mediated inhibition of LSCs involves the interleukin-6 (IL-6) and sonic hedgehog (Shh) signaling axis. IL-6 and Shh molecules are important to maintain the growth and expansion of LSCs [41–43]. Recently, Su and coworkers have identified that the IL-6 in plasma, Shh pre-proteins, C- and N-terminal Shh peptides in bone marrow and peripheral blood mononuclear cells in patients with AML are much higher than those in healthy individuals. In this study, the authors showed that resveratrol significantly reversed the elevated Shh expression, Gli-1 nuclear translocation, and cell viability in IL-6-treated leukemia cells.

Chronic myeloid leukemia (CML) has long been considered to be a stem cell disease characterized by the BCR-ABL gene rearrangement [44]. However, the influence of resveratrol or pterostilbene on CML is still unknown. Tolomeo et al. reported that pterostilbene has a greater capacity to induce CML cell apoptosis than resveratrol because of its unique methoxyl structure [45]. Cell apoptosis induced by pterostilbene could not be suppressed by the pan caspase-inhibitor Z-VAD-fmk, indicating that a caspase-independent signaling pathway may be related to LSCs apoptosis. Interestingly, it seemed that pterostilbene induced apoptosis specifically in LSCs, as it displayed no cytotoxicity in normal hemopoietic stem cells. These results indicate an exploitable therapeutic potential of pterostilbene in LSCs.

2.3. Colorectal stem cells

Globally, colorectal cancer is high incidence malignant tumor type. In pathology, colorectal cancer starts from the epithelial cells lining the colon or rectum. Several studies have indicated that mutations in the Wnt/β-catenin signaling pathway occurring in the intestinal crypt stem cells play a critical role in maintenance of cancerous proliferation and stemness activity in colorectal stem cells (CSCs) [46,47].

Many studies have been done with resveratrol to target CSCs. Although sporadic pterostilbene prevention of colon cancer has been reported, there are almost no documents regarding pterostilbene against CSCs to date. Utilizing a grape seed extract supplement regimen (resveratrol -GSE), Reddivari et al. [12] identified that resveratrol -GSE suppressed diazoxymethane-induced colon cancer incidence in a rodent model. The pathological data indicated this regimen increased

apoptosis and decreased number of crypts with CSCs. More importantly, resveratrol -GSE preferentially suppressed downstream proteins of the Wnt/β-catenin signaling pathway, such as c-Myc and cyclin D1, compared with the non-steroidal anti-inflammatory drug sulidac, which has shown promising characteristics against colon cancer. Another report from Reddivari et al has shown that resveratrol -GSE also induced mitochondrial-mediated apoptosis in colon CSCs characterized by elevated p53, Bax/Bcl-2 ratio, and cleaved PARP.

2.4. Glioblastoma stem cells (GSCs)

Glioblastomas are also one of the leading causes of death by cancer in adults. In addition to the relative hidden location where drugs are difficult to deliver, glioblastoma harbors a small group of GSCs associated with therapy resistance and tumorigenesis.

Recent studies have shown that resveratrol has negative impacts on GSCs. Sayd et al. found that resveratrol could inhibit proliferation and start necrosis in GSCs [25]. Interestingly, resveratrol intercellular adaptor sirtuin-2 (SIRT2) only acts on GSCs proliferation, but blockade of SIRT2 has no effect on cell necrosis induced by resveratrol. Another study performed by Wang et al showed that resveratrol down-regulated the stem cell marker CD133 in SU-2 glioblastoma cells and inhibited clonogenic survival. When combined with ion radiation, resveratrol significantly improved the therapeutic sensitivity of GSCs both in vitro and in vivo.

Cilibrasi et al. investigated the efficacy of resveratrol on GSCs using seven established lines, which possess extensive stem-like properties [27]. In these researchers' studies, resveratrol generally decreased GSCs viability and proliferation and inhibited GSCs motility and invasion. Furthermore, the authors identified that resveratrol conditionally inhibited the Wnt signaling pathway activity that plays a key role in the regulation of CSC stemness and metastasis and down-regulated two key activators of EMT, Twist1 and Snail1. Although GSCs respond heterogeneously to resveratrol, these researchers postulated that resveratrol remains a promising approach to target GSCs.

The mechanism of targeting GSCs by pterostilbene may be involved in an antistress protein GRP78. Glioblastoma multiforme (GBM) is the poorest prognostic type. GRP78 highly expressed in GBM cells and promotes β-catenin and Notch signaling pathways, which are strongly linked with stemness and the development of $CD133^+$ GSCs. pterostilbene treatment suppresses GRP78 and stemness pathways to lead to decreased stemness activities and increased γ-radiation sensitivity in GSCs. Mechanistically, pterostilbene treatment counteracts the expression of GRP78 and c-myc through upregulation of miroRNA205.

2.5. Head and neck CSCs

Similar to CSCs mentioned above, Hu and colleagues investigated resveratrol treatment of tumor-initiating stem cells from head and neck cancer and found reduced sphere-forming primed by stemness factors (oct4, nanog, and nestin), malignant properties, including EMT markers (N-cadherin, Slug, ZEB1, E-cadherin, and Vimentin), and invasiveness or anchorage-independent growth. Importantly, an in vivo xenograft tumor model performed by the authors is consistent with the in vitro observations [29].

Because of the undifferentiated features, anaplastic thyroid cancer (ATC) is a term for an aggressively lethal cancer for which conventional therapies are usually ineffective. Hardin et al. isolated and generated two clonal spheroid CSC lines from this type of cancer and observed that resveratrol treatment reduced the expression of two new stem cell markers, stage-specific embryonic antigen 1 (SSEA1), and aldehyde dehydrogenase (ALDH), in addition to NANOG, OCT4, and SOX2. Moreover, resveratrol treatment was found to lead to the expression of two differentiation markers, TTF1 and sodium iodide symporte, in ATC cells via activation of Notch1 signaling [48].

In a nasopharyngeal carcinoma model, Shen et al. found that resveratrol suppressed stemness properties and metabolic reprogramming of CSCs through reactivating p53 and inducing miR-145 and miR-200c. Hence, further investigation of the p53 signaling pathway may provide promising development of novel therapies for nasopharyngeal carcinoma [32].

2.6. Impacts of resveratrol and ptereostilbene on other types of CSCs

Emerging reports indicate resveratrol and ptereostilbene have even a broad spectrum of CSC prevention in addition to the types of CSCs mentioned above Ovarian cancer is one of the lethal gynecological malignancies in women because of the poor prognosis attributed primarily to fatal recurrence [49]. Resveratrol was reported to target ovarian CSCs via both reactive oxygen species (ROS)-dependent and -independent pathways [31]. ROS play a critical role in mediating the loss of the self-renewal capacity when ovarian CSCs are treated with resveratrol. However, it seemed that ROS may not be required for RES-induced death of ovarian CSCs. Melanocyte hormone (α-MSH) signaling pathways, including c-Kit, Wnt/β-catenin, and microphthalmia-associated transcription factor (MITF), are highly bound up with melanoma CSC characteristics [33]. Resveratrol alone or combined with tyrosine kinase inhibitor imatinib mesylate may impede melanoma CSC-associated signaling molecules and then inhibit the melanogenesis process and CSC characteristics of melanoma [33].

Lee et al. isolated pterostilbene from blueberry and investigated its potential function on irradiation-mediated enrichment of hepatoma CSCs. In these studies, pterostilbene was observed to increase apoptosis and lower the enrichment of $CD133^+$ Mahlavu cells resulting from irradiation. Furthermore, pterostilbene treatment also blocked the properties of CSCs, including sphere formation, stemness genes expression, and invasive capacity [34].

Regarding lung CSCs (LCSCs), Huang et al. identified that pterostilbene may disturb the interaction between LCSCs and M2-polarized tumor-associated macrophages (M2-TAM) via modulating pro-oncogenic MUC1 signaling pathway. The

authors observed that MUC1 secreted by M2-TAMs promotes the generation of $CD133^+$ LCSCs and stemness abilities in addition to increasing NF-κB associated inflammation. Hence, pterostilbene prevented MUC1 expression in TAM and led to decreased M2-TAM polarization and reduced generation and malignant phenotypes of LCSCs. This research suggested that alteration of the tumor microenvironment may abate the malignant behavior of LCSCs [35].

3. Conclusions

Despite advances in variety of cancer treatment solutions, the prognosis of the patients suffering from advanced cancer is still very poor. Targeting CSCs may represent a potential therapeutic approach. Natural product compounds, such as resveratrol or pterostilbene, received some attention because of their profound modulation of various types of CSCs in addition to low toxicity to human beings. In summary, we predict that exploring the interactions between CSCs and phytochemicals, including key signaling pathways and molecular targets, will contribute to the development of novel anticancer agents and appropriate clinical trials for cancer therapy.

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