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Review

Natural Products That Target Cancer Stem Cells

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Abstract. *The cancer stem cell model suggests that tumor initiation is governed by a small subset of distinct cells with stem-like character termed cancer stem cells (CSCs). CSCs possess properties of self-renewal and intrinsic survival mechanisms that contribute to resistance of tumors to most chemotherapeutic drugs. The failure to eradicate CSCs during the course of therapy is postulated to be the driving force for tumor recurrence and metastasis. Recent studies have focused on understanding the unique phenotypic properties of CSCs from various tumor types, as well as the signaling pathways that underlie self-renewal and drug resistance. Natural products (NPs) such as those derived from botanicals and food sources may modulate vital signaling pathways involved in the maintenance of CSC phenotype. The Wingless/Integrated (WNT), Hedgehog, Notch and PI3K/AKT/mTOR pathways have all been associated with quiescence and self-renewal of CSCs, as well as execution of CSC function including differentiation, multidrug resistance and metastasis. Recent studies evaluating NPs against CSC support the epidemiological evidence linking plant-based diets with reduced malignancy rates. This review covers the key aspects of NPs as modulators of CSC fate.*

In spite of an expansive array of available chemotherapeutic (CT) drugs and vastly improved diagnostic technologies, overall the five-year survival rates for all cancer types in the U.S. have only risen from 50% in the 1970s to about 65% today (1). The therapeutic efficacies of most CT drugs are severely hampered by toxicity profiles that limit their life-extending potential. New technologies aimed at improving the performance of CT drugs such as drug delivery systems and chemosensitizers have been slow to show clinical promise in most types of cancer. The failure to significantly improve cancer survival rates suggested that there are more fundamental 'upstream' therapeutic targets during the carcinogenesis process than those that respond to CT drugs in differentiated tumor cells. This led to the cancer stem cell (CSC) hypothesis, which predicted that cancer arises in genetically aberrant cells with tumor-initiating properties and stem-like character akin to normal stem cells (2). The viewpoint of cancer as fundamentally a stem cell disease represents an important paradigm shift in our conceptual understanding of carcinogenesis and tumor biology and has ushered in a new era that challenges the dogmatic approaches to cancer cell destruction. Aberrant gene-expression profiles long considered hallmarks of malignancy has been re-evaluated in the context of the CSC with emphasis on genes that regulate self-renewal processes and differentiation programs which are normally tightly regulated in the non-cancerous somatic stem cell. As a result, there is an urgent need to identify compounds that strike targets involved in CSC self-renewal and differentiation programs, respectively.

A straightforward approach to targeting CSC self-renewal and differentiation programs may be the use of chemopreventive natural product (NP) compounds often found in dietary sources. The potential for dietary NPs to guard against malignant transformation of cells is supported by a plethora of epidemiological evidence that shows a strong correlation between consumption of plant-based diets with reduced cancer risk (3). Efforts are underway to identify and characterize the mechanistic pathways by which various NPs inhibit CSC self-renewal and differentiation programs with the ultimate goal of establishing therapeutic regimens that can prevent tumorigenesis or tumor recurrence and improve patient survival.

This review covers the key properties of CSCs, including self-renewal programs, differentiation programs, survival pathways, detoxification mechanisms and other putative mechanisms involved in cancer relapse, that are potentially amenable to therapeutic intervention using NPs. CSC survival and proliferative pathways that include Wnt/β-catenin, Hedgehog, Notch and PI3K/AKT/mTOR are reviewed to

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highlight potential key targets for therapeutic intervention. The modulation of detoxification mechanisms including multidrug resistance (MDR) in CSCs by NPs is also addressed. The basis of plant-derived NP activity is considered, highlighting the role of evolutionary pressure in the formation of pharmacologically active compounds. We conclude with a description of select NP compounds grouped by chemical class that have shown activity in regulating CSCs either directly or which have exhibited activity in CSC-associated pathways.

Therapeutic Implications of CSCs in Cancer Treatment

The failure to assess CSC response in patients receiving CT may be a factor contributing to tumor recurrence, as suggested by numerous retrospective studies challenging current Response Evaluation Criteria in Solid Tumors (RECIST) guidelines for evaluating the efficacy of cancer therapeutics in clinical trials (4). Specifically, the time-to-progression, progression-free survival and tumor size criteria for evaluating therapeutic efficacy of drug compounds have been individually and collectively challenged for not accurately reflecting patient outcome. As a result, new guidelines for standardizing and evaluating response criteria in established stem cell-associated malignancies are being proposed (5).

There exist a number of intrinsic drug-resistance mechanisms in CSCs which can inactivate cytotoxic drugs, resulting in tumor recurrence (6). Most CT drugs effect apoptotic response in differentiated tumor cells, thereby conferring CSCs with a survival advantage with even greater proliferative potential (7). The result is that tumor cells repopulate with lineage-dependent genotypic and phenotypic alterations, including MDR, that render CT drugs ineffective and lead to more rapid disease progression and poorer prognoses (8). Furthermore, hypoxic stability of CSCs enables them to survive in poorly vascularized microenvironments that challenge drug accessibility to niche networks and contributes to MDR (9).

If indeed the CSC response is a vital criterion for cancer treatment evaluation, there are still no drugs in clinical use that specifically target CSCs. Developing CSC-specific drugs is complicated by the genotypic variability of CSCs and genomic instability of hyperplastic progeny that makes karyotyping of tumor cell populations enormously challenging (10). Targeting CSC self-renewal programs using agents such as NPs ahead of differentiation programs may prevent the development of MDR-associated mutations during tumor growth that lead to refractory response to treatment (11). NPs have shown promising effects in sensitizing CSCs to CT by targeting molecular signaling pathways that modulate stemness properties in a broad spectrum of cancer types (12). Thus, NPs may be combined with conventional CT drugs to form potent dual-target therapies against CSCs and differentiated tumor cells.

Genetic and Molecular Signatures of CSCs

Specification of the CSC genotype and phenotype assists in the identification of potential molecular targets for screening of NPs for therapeutic activity, and may lead to prognostic markers of tumor recurrence and metastasis (13). Methods for identifying CSCs include analysis of surface Cell Adhesion Molecules (CAM) expression (immunophenotype) profiles including CD133, CD44, CD34, CD24 using Fluorescence Activated Cell Sorting (FACS) (14), immunofluorescent detection by confocal microscopy (15), tumor sphere-forming assays (16), Hoechst dye exclusion in side-population (SP) cells (17), detection of enzymatic activity of Aldehyde Dehydrogenase 1 (ALDH1) (*e.g.* Aldefluor assay) (18), signaling pathway identification, serial colony-forming unit assays (19), migration assays (20) and label-retention assays (21). Identification of CSCs using these methods can reveal differentially expressed stemness markers which are often associated with MDR. Expression of detoxifying enzymes such as ALDH1 (22), increased expression and activity of drug efflux transporters of the MDR-ATP-Binding Cassette transporters (ABC) family such as ABCG2 (BRCP) (23), expression of other anti-apoptotic factors associated with drug resistance including B-Cell Lymphoma (BCL): BCL2, BCL-xl, survivin and Macrophage Inhibitor Cytokine 1 (MIC1) (24) and activation of transcription factors such as Octamer-binding transcription factor-4 (OCT4), SRY (sex determining region Y)-box 2 (SOX2) and NANOG which drive expression of genes regulating pluripotency (25). Amplification of checkpoint activation and efficient repair of DNA and oxidative damage *via* constitutive activation of Nuclear Factor-kappa B (NF-κB) and expression of CD133/prominin-1 have also been suggested as CSC biomarkers.

Alkaline phosphatase (ALP) is a ubiquitously expressed hydrolase enzyme that de-phosphorylates a variety of substrates and is a marker of many urological disease states and various types of cancer. One of the most-studied of the ALP isoenzymes is the Regan isoenzyme (placental ALP, ALPP) first described by Fishman (26). ALPP is highly expressed in colon cancer (27), renal carcinoma (28) and metastatic melanoma (29). In stem cells, ALP serves as a useful differentiation marker as the enzyme is significantly down-regulated during maturation of cell lineages (30). Liu *et al.*, compared two ovarian CSC populations from human patient distinguished by differentiation capacity in tumor sphere assays (25). The more aggressive CSC phenotype (with sphere-forming capacity) expressed higher levels of ALP than CSCs with lower sphere-forming potential, whereas ALP was not expressed in differentiated progenies lacking stemness properties. Total serum ALP may also facilitate prediction of cancer course and prognosis. Kim *et al.*, performed a retrospective study of 238 patients with bone metastatic prostate cancer and found that total serum ALP levels exhibited

a very strong correlation with likelihood of metastasis whereas falling ALP was a positive prognostic sign (31).

Epithelial Mesenchymal Transition (EMT) is a differentiation program in which epithelial cells transform into more motile and fibroblast-like cells with mesenchymal character and leads to reconstitution of tumors in new vascular niches (32). Recent evidence points to molecular links between genes associated with CSC self-renewal programs and EMT-associated transcription factors (33). Enhanced expression of hypoxia factors Hypoxia-Inducible factor-1α (HIF1α) and HIF2α in CSC/progenitor cells frequently occurs during disease progression and metastasis and a molecular link between hypoxic stability and up-regulated stemness-related gene products and pro-survival elements has been established (34). Indeed many of the altered gene products modulated by HIFs in CSCs also factor in the MDR phenotype including ABCB2, BCL2, BCl-xL, survivin and MIC1, transcription factors OCT3/4, SOX2 and NANOG, pro-angiogenic factors such as Vascular Endothelial Growth Factor (VEGF) (35), EMT markers including Epidermal Growth Factor Receptor (EGFR), C-X-C Chemokine receptor type 4 (CXCR4) (36), Zinc finger protein SNAI1 (SNAIL) and TWIST(37), Glucose Transporter 1/2 (GLUT1/2), cell-cycle regulation (38), altered metabolic pathways such as glycolytic enzymes (39), and microRNAs (miRNAs) (40). Thus, identification of CSC gene-expression patterns associated with EMT may identify the mechanisms and specific CSC development and maintenance programs that have become dysregulated and contribute to the metastatic potential of various types of cancer.

Ultimately, *in vivo* stemness assays such as serial transplantation in animal models are required to corroborate stemness markers identified through *in vitro* assays, permit evaluation of the effects of stemness markers on tumor properties and allow for screening of NPs for therapeutic activity in CSC populations (14).

Drug Efflux and Detoxification Mechanisms

MDR-ABC transporters. In the CSC model, drug resistance develops when progenitor cells survive drug exposure and differentiate into lineages bearing assorted mutations exhibiting the MDR phenotype. MDR in CSCs can result from a variety of metabolic and transport-associated resistance mechanisms to cytotoxic drugs that include drug efflux, alteration of cellular targets, reduced drug uptake and transport, enhanced drug metabolism and inactivation by enzymes (41). Inhibition of MDR/ABC efflux pumps is a potential therapeutic approach for targeting CSCs. Certain NPs exhibit high potency and specificity for MDR-associated transport proteins such as lung-resistance proteins (LRPs) and ABC transporters which are often overexpressed in CSCs (42). NPs may re-sensitize MDR cells to CT drugs by inhibiting efflux activity of the drug pump, or alternatively by down-regulation of gene expression (43). ABC targets for NPs can include *ABCB1, ABCB5, ABCG2* and *ABCC1* genes or their products which are commonly differentially expressed in stem-like versus differentiated tumor cell types (44). Factors such as pluripotency and plasticity of differentiated tumor cell phenotype may contribute to considerable ABC gene expression heterogeneity amongst tumor types and must be considered when evaluating prospective NP compounds for efficacy (45).

P-Glycoprotein is a multidrug efflux transporter product of *ABCB1* gene expression. Many NPs have inherent ABCB1 inhibition properties likely as a consequence of evolutionary co-development in the same plant species. Adaptation of P-glycoprotein in herbivores to harmful plant natural products resulted in plant production of secondary metabolites that in turn inhibit P-glycoprotein for self-defense. Hence, it can be speculated that P-glycoprotein inhibitors should be present in plants and belies much of the basis of traditional Chinese medicine (46).

ABCG2 is also an important molecular target as this transporter is commonly overexpressed in many human cancer types (47). ABCG2 has been shown to play a critical role in clinical resistance of tumors to anticancer drugs suggesting CSC involvement (48). ABCG2 is a 72-kDa protein whose gene expression is regulated by numerous growth- and survival-linked cellular transcription factors including NF-κB, HIF1α, EGFR, cAMP Response Element Binding Protein (CREB), Signal Transducer and Activator of Transcription (STAT) and others regulatory elements within the ABCG2 promoter region including have been identified at -312/+362 upstream of the transcriptional start site of the human *ABCG2* gene (46). Specific NPs targeting ABCG2 and other important resistance proteins are discussed below.

Detoxifying enzymes. The ALDH family of NAD $(P)^+$-dependent enzymes catalyze the oxidation of aldehydes into carboxylic acids. ALDH1 and other isoforms play a critical functional role in drug detoxification in CSCs that contribute to their survival, differentiation and self-renewal in various cancer types (49). Chemosensitization of tumor cells using the established ALDH inhibitor diethylaminobenzaldehyde (DEAB) was shown to sensitize resistant $ALDH^{hi}/CD44^+$ stem-like breast cancer cell lines to CT drugs and radiotherapy (50). However, DEAB is limited to *in vitro* assays due to its lack of ALDH isoform-specific activity and high toxicity. NPs have been suggested as an alternative for blockade of ALDH1 activity and to sensitize CSCs to CT drugs (51). NPs with purported ALDH-inhibitory activity include citral, gossypol, daidzin and coprine though screening of these compounds for activity in stem-like cells has not been reported. Cytochrome *P450* (CYP450) enzymes are an evolutionary conserved superfamily of hemoproteins whose concomitant expression with P-glycoprotein are believed to be an important

evolutionary adaptation against potentially toxic substances. CYP450 may play a pivotal role in chemoprevention of malignancies. CYP enzymes can also metabolically activate carcinogenesis by converting procarcinogens to carcinogens. For example, CYP450 isoforms involved in steroid or retinoic acid metabolism could promote or suppress tumour development through hormonal control (52). Dietary consumption of foods enriched in phytochemicals with CYP450-inhibitory activity has long been associated with anticancer and chemopreventative properties (53). Phytochemicals may also exert action by binding to various functionally diverse cellular targets which epigenetically regulate downstream metastasis suppressing genes (54). Dietary phytochemicals include species such as phytoalexins, flavonoids, terpenes, glycosides, carotenoids, phytosterols, and many others.

Genetic variability may also play a role in tumor development as certain CYP allelic variants can influence the bioactivation of carcinogens and serve as biomarkers for cancer susceptibility. For example, CYP1B1 plays an important role in the bioactivation of carcinogens in different cancer types. CYP1B1 is highly expressed in mammary, ovarian and uterine tissue, where it catalyzes the 4-hydroxylation of estradiol, which can generate free radicals that cause cellular damage and may lead to breast and endometrial carcinogenesis (55). Other CYP1 enzymes such as CYP1A1 and CYP1A2 can also be activated by procarcinogens such as polycyclic aromatic hydrocarbons, nitrosamines and arylamines, which are associated with cancer of the bladder, head and neck where polymorphic variants of these enzymes are often expressed. Phytoalexins are parasite-resisting compounds with antimicrobial and antioxidative properties that comprise part of immune systems of many plants species. Salverastrols are phytoalexins that have been shown to have potent activity against CYP1 enzymes (56). Investigation of plant polyphenols as chemopreventative compounds against new molecular and cellular targets including CYP1 enzymes, epidermal stem cells, cellular senescence, epigenetic enzymes involved in carcinogenesis have been suggested and infer a potential cytoprotective role against malignant transformation of stem cells.

Developmental and Maintenance Signaling Pathways

Our understanding of the development and maintenance signaling pathways used by CSCs is confounded by the fact that the origin of the CSC itself is still under considerable speculation. One view is that the development of genetic instability in normal somatic stem cells results in dysregulation of the self-renewal program and imparts tumorigenicity to the cells. Alternatively, CSCs may be derived from differentiated tumor cells through the acquisition of multiple oncogenic mutations of genes that confer stemness properties on cells by way of a phenomenon referred to as plasticity of phenotype (57). Nevertheless, evidence has linked dysregulation of key regulatory stemness signaling pathways common to embryonic development and tissue homeostasis to CSCs (58). Self-renewal and quiescence are two key hallmark properties of CSCs and somatic stem cells alike. In normal stem cells, self-renewal is under tight regulation by transcription factor-mediated pathways that respond to extrinsic growth factor signals as part of the signal transduction process. On the other hand, dysregulation of transcription factor expression or activity in CSCs can promote abnormal self-renewal response that contributes to tumor progression as the neoplastic cells differentiate into more highly proliferative tumor cells. The major mechanistic routes exploited by CSC for these pro-survival signaling and self-renewal are the WNT/β-catenin, Hedgehog, Notch and PI3K/AKT/mTOR pathways, are presented here.

WNT/β-catenin pathway. The WNT/β-catenin signaling pathway modulates cell proliferation, migration and apoptosis in differentiated cancer cells and has been implicated in the maintenance of CSC self-renewal in various cancers (3). WNT/β-catenin signaling is initiated on binding of WNT to Frizzled receptor resulting in cytoplasmic accumulation of β-catenin. In the non-pathological state, β-catenin is sequestered at the cell membrane by the epithelial cell adhesion protein E-cadherin to maintain cell–cell adhesion (59). In the absence of WNT signaling, β-catenin forms a multi-protein complex with glycogen synthase kinase 3β (GSK3β), adenomatous polyposis coli, casein kinase 1α, and axin. GSK3β plays a central role in controlling the activity of the WNT/β-catenin pathway by regulating β-catenin stability and degradation. GSK3β-dependent phosphorylation of β-catenin at Ser33/Ser37/Thr41 restricts its nuclear translocation by inducing ubiquitin-proteasome degradation (60). Activated β-catenin complexes recruit transcriptional co-activators CREB binding protein (CBP) and p300 that regulate expression of downstream WNT target genes.

β-Catenin nuclear translocation and activation of target genes is also associated with other transcription factor complexes including T-cell factor/lymphoid enhancer factor (TCF/LEF). Thus, GSK3β acts as a tumor suppressor by curbing canonical WNT/β-catenin signaling. The WNT/GSK3β/β-catenin signaling axis has been linked with self-renewal of both normal stem cells and CSCs. Suppression of GSK3β activity was shown to be critical for maintenance of murine pluripotent stem cells (61). Inactivating mutations of GSK3β have been associated with faulty CSC development programs in Breakpoint Cluster Region-Abelson (BCR–ABL) chronic myeloid leukemia (CML), corroborating earlier findings that associated nuclear accumulation of β-catenin in BCR–ABL CSCs with progression of the disease. Mouse

xenografts of pre-leukemic and leukemic stem cells of mixed-lineage myeloid leukemia (MML) exhibited differential WNT/GSK3β/β-catenin signaling including elevation of β-catenin levels in the tumorigenic CSCs that resulted in enhanced self-renewal, higher tumor relapse rates and poorer survival outcomes than MLL pre-leukemic CSCs (62). Overexpression of β-catenin has been shown to cause resistance of CSCs to radiation and chemotherapy in mouse and rat xenografts, respectively (63). Yang *et al*., demonstrated that introduction of constitutively active β-catenin (S37Y) in tumorigenic hepatocellular carcinoma cells imparted cisplatin chemoresistance, whereas elimination of β-catenin virtually abrogated the chemoresistant cell population endowed with progenitor-like features (64).

Hedgehog. The Hedgehog family of signaling molecules normally function tissue development by regulating cellular differentiation and proliferation. The Hedgehog pathway is an important cancer target as dysregulation of Hedgehog is found in a wide variety of cancer types. Although several Hedgehog-inhibitory drugs are approved or presently under clinical development, it has been reported that these drugs may actually promote drug-resistant tumors, potentially due to CSC selection (65).

The transcription factor NF-κB is a downstream factor activated by the Sonic Hedgehog (Shh) pathway in pancreatic cancers (66). In human leukemia, $CD34^+$ sub-population exhibits the preponderance of Hedgehog signaling. Su *et al*., examined the role of Shh in survival and growth of Chronic myeloid Leukemia (CML) progenitor cells (67). Low level of Shh protein was observed in CML bone marrow stromal cells. This was associated with $CD34^+$ progenitor cells that were less sensitive to exogenous Shh peptide, but more sensitive to cyclopamine than $CD34^-$ cells. This implies that activation of Shh signaling can occur autonomously in progenitor cells.

Notch pathway. The Notch signaling pathway is a highly evolutionarily conserved component involved in the maintenance of cell diversity and stem-cell self-renewal (68). Four known Notch proteins, Notch1 to Notch4, reside as transmembrane receptors in various stem and progenitor cells. Activation of Notch signaling occurs *via* binding of Delta-like and Jagged surface ligands, which triggers cleavage by A Disintegrin and Metalloproteinase (ADAM) proteases and secretase proteolytic enzymes (69). The Notch intracellular domain is released in the process and functions as a transcription factor for various genes promoting proliferation including *c-Myc*, cyclin D1, *p21*, NF-κB (70). Functional cross-talk between Notch and NF-κB pathways was shown to be active in hyperproliferative colon cancer (2). In a recent intriguing study, highly regenerative prostate luminal epithelial progenitor cells were shown to exhibit enhanced proliferation *via* Notch signaling that promoted metastatic effects by inhibition of anoikis (71). Markstein *et al*. (72) developed a systematic method to screen small molecules against CSC populations using a Drosophila model. Drosophila intestinal stem cells are multipotent and give rise to cell types similar to mammalian CSC. Most importantly, both mammalian CSC and Drosophila stem cells act through evolutionarily conserved pathways including EGFR, HIPPO, AKT and Janus Kinase (JAK)-STAT, which enable us to screen CT agents using drosophila as a model.

PI3K/AKT/mTOR and crosstalk. The PI3K/AKT/mTOR axis is a central intracellular signaling pathway regulating cellular apoptotic function. PI3K/AKT/mTOR plays a key role in many cancers owing to the high frequency of mutation to the tumor suppressor gene phosphatase and tensin homolog (*PTEN*), which regulates PI3K signaling. Unrepressed PI3K signaling results in constitutive activation of downstream pathway components that include the AKT and mTOR kinases and drive a host of cellular pro-survival adaptations (73). PTEN loss has been shown to mediate AKT activation and increase stemness properties of CSC populations in prostate cancer (74). Furthermore, crosstalk between PI3K/AKT and other pro-survival as well as mitogenic pathways has been shown to drive cancer growth (75). Inactivation of GSK3β by AKT may result in down-regulation of WNT, Hedgehog, and Notch signaling pathways (76). Crosstalk has been demonstrated to regulate activity of mammary stem/progenitor cells through GSK3β abrogation and β-catenin activation of downstream events (77). Crosstalk between tyrosine kinase receptors, GSK3β and Bone Morphogenetic Protein 2 (BMP2) signaling during osteoblastic differentiation of human mesenchymal stem cells was observed (78). It was suggested that PI3K signaling together with nuclear accumulation of β-Catenin is necessary to fully activate canonical WNT signaling in colon cancer and correlated with a high risk of distant metastasis in patients with colon cancer (79).

NPs as Modulators of CSC Pathways

Modulation of ABC transporters. NPs that have been evaluated directly in assays of activity in CSCs, or have shown strong evidence of activity against specific targets in CSC renewal or differentiation-associated pathways are shown in Table I and Figure 1.

Many phytochemicals including carotenoids, capsanthin and capsorubin, lycopene, lutein, antheraxanthin, violaxanthin and flavonoids (rotenone, chrysin, phloretin and sakuranetin) and various traditional chinese medical herbs, exhibit ABCB1- and ABCG2-modulating activity (80). The phytoalexin, allixin, isolated from garlic has shown anti-tumor-promoting effects *in vivo*, inhibiting skin tumor formation by Tissue Plasminogen Activator (TPA) in 7,12-Dimethylbenz[a] anthracene (DMBA)-initiated mice.

Table I. *Natural products with reported activity towards cancer stem cells and related mechanisms*.

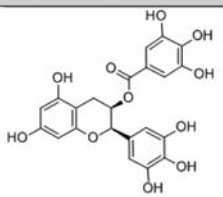
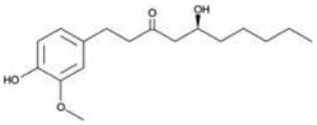
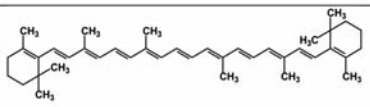
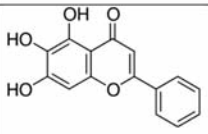
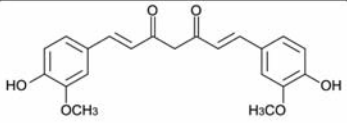
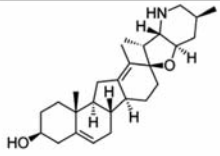
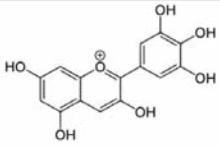
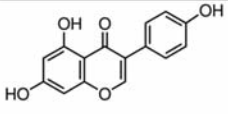
Compound	Structure	Source	Cancer cell type	Target
(−)-Epigallocatechin-3-gallate		Green tea	Breast CSC, colon CSC, pancreatic CSC	cyclinD1, BCL-XL, HBP1, AKT, HSP90
6-Gingerol		Ginger	Colon	WNT/β-catenin TNF, NFκB, AP1
β-Carotene		Potato, carrot, leafy greens	Neuroblastoma	HIF1α, OCT3/4, DLK1
Baicalein		*Scutellaria baicalensis*	Bone marrow, CML CSCs	ABCG
Curcumin		Turmeric	Breast, brain, colon, pancreas	WNT/β-catenin, Hh, Notch, ABCG1, ABCB1, ABCC1
Cyclopamine		Corn lily	Breast CSC, bone marrow, CML CSC	Hh, Smo
Delphinidin		Blueberry, raspberry	Neuroblastoma	WNT/β-catenin, Hh, Notch
Flavanoids (Genistein)		Soy, legumes	Breast CSC, ovarian SC, kidney, melanoma	WNT/β-catenin, Hh, Notch

Table I. *Continued*

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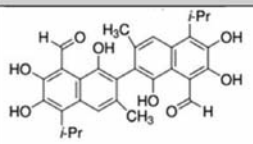
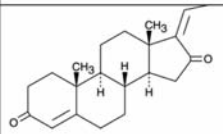
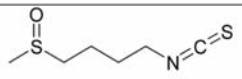
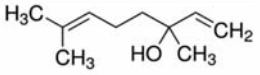
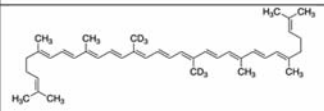
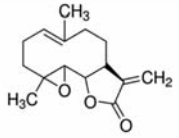
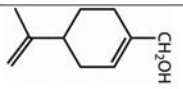
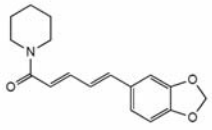
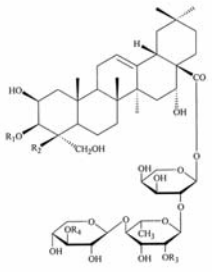
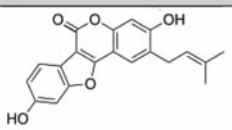
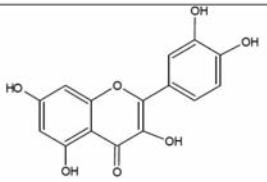
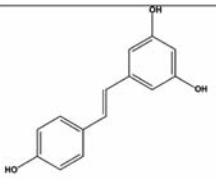
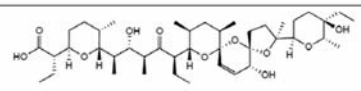
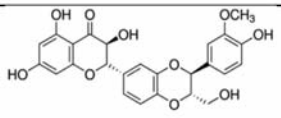
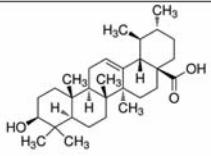
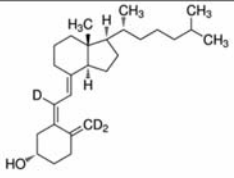
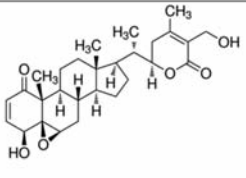
Compound	Structure	Source	Cancer cell type	Target
Gossypol		Cottonseed	Prostate CSCs	DNA damage, p53 activation, apoptosis
Guggulsterone		Commiphora mukul tree	Murine breast CSCs	$CD44^{+}$, apoptosis - caspase-3, ceramide
Isothiocyanates (R- sulforaphane isothiocyanate)		Cruciferous vegetables	Prostate, pancreas, cervix	NFκB, AKT/PKB, miR-LET7
Linalool		Mint, various herbs	AML	G_0/G_1, NFκB, p53
Lycopene		Tomatoes, grapefruit	Breast CSC	WNT/β-catenin, Hh, Notch
Parthenolide		Feverfew	Breast CSCs, AML CSCs, lung	NFκB, TNFRSF10B, PMAIP1
Perillyl alcohol		Mint, cherry, lavender	Burkitt's lymphoma, lung	Cell cycle arrest, NFκB
Piperine		Black pepper, Long pepper	Breast CSCs	WNT/β-catenin
Platycodon saponin		*Platycodon grandiflorum*	Prostate	PI3K/AKT, ERK1/, SMAD

Table I. *Continued*

Table I. *Continued*

Compound	Structure	Source	Cancer cell type	Target
Psoralidin		*Psoralea corylifolia*	Prostate	PI3K/AKT, Notch1
Quercetin		Capers, pepper	Breast, oral CSCs, pancreas, colon	WNT/β-catenin, Hh, BCL/BAX, MAPK, LET7, KRAS
Resveratrol		Grapes, plums, berries	Mammospheres, medulloblastoma CSCs, colon	Apoptosis, DAPK, BNIP3, lipid synthesis, fatty acid synthase Proliferation, radiosensitivity
Salinomycin		*Streptomyces albus*	Breast, cervical, prostate, colon	WNT/β-catenin, mTOR, CD133
Silibinin		Milk thistle	Breast, lung, prostate, colon	WNT/β-catenin, Notch1, Hh, CD133
Ursolic acid		Thyme, basil, oregano	Breast, colon, prostate	WNT/β-catenin, Notch1, Hh, PI3K/AKT
Vitamin D_3		Fish, egg yolk, beef	Breast CSC, basal cell carcinoma	CD44, WNT/β-catenin
Withaferin A		*Withania somnifera*	Breast CSC	Notch1

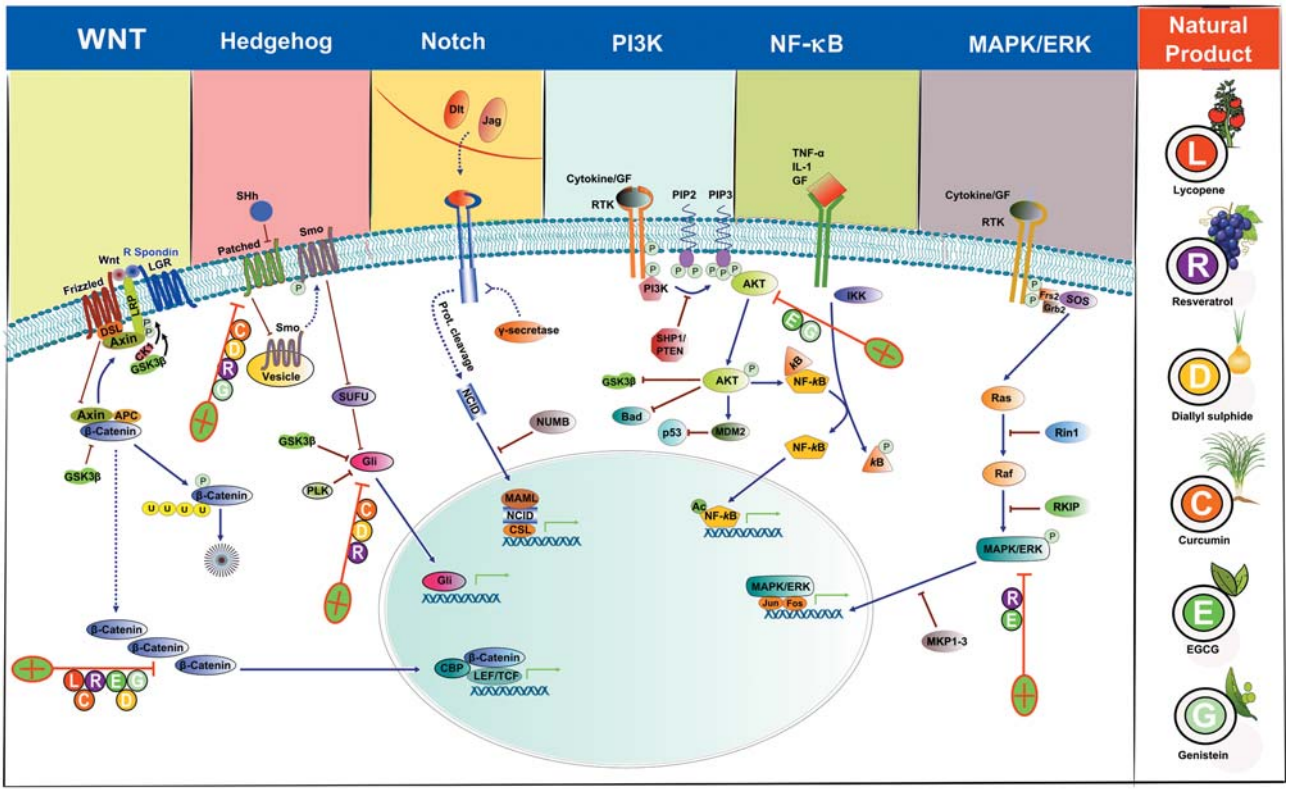


Figure 1. *A schematic representation of molecular signaling of cancer stem cell (CSC) and the effect of natural compounds on these molecular targets. ABC; Adenosine triphosphate (ATP)-binding cassette, ABCB1/G2; ABC subfamily B/G member ½, AP1; activator protein 1, BAD; BCL2-Associated Agonist Of Cell Death, APC; Adenomatous Polyposis Coli, BCL_{XL}; B-cell lymphoma-extra-large, BNIP3; BCL2/Adenovirus E1B 19kDa Interacting Protein 3, CSC (s); cancer stem cell (s), DAPK1; death-associated protein kinase 3, DLK1; Delta-Like 1 Homolog, GRB2; Growth Factor Receptor-Bound Protein 2, GSKb; Glycogen Synthase Kinase 3 Beta, Hh; Hedgehog,FRs2: Fibroblast Growth Factor Receptor Substrate 2, FN1; Fibronectin 1, HBP1; HMG-Box Transcription Factor 1, HSP90; heat shocking protein-90, IKB; Inhibitor Of Kappa Light Polypeptide Gene Enhancer In B-Cells, JUN; Jun Proto-Oncogene, LGR4; Leucine-Rich Repeat Containing G Protein-Coupled Receptor 4, MAML1; Mastermind-Like 1, MAPK; Mitogen-Activated Protein Kinase 1, MDR, multi-drug resistance; OCT-1; octamer-binding transcription factor 1,p53: protein 53 PI3K; Phosphatidylinositol-4,5-Bisphosphate 3-Kinase, Catalytic Subunit Alpha, PTEN; Phosphatase And Tensin Homolog RAS; Rat Sarcoma Viral Oncogene Homolog, RIN1; Ras And Rab Interactor 1, RAF1; Raf-1 Proto-Oncogene, Serine/Threonine Kinase, STAT; Signal transducer and activator of transcription; SMO; Smoothened, Frizzled Class Receptor, SUFU; Suppressor Of Fused Homolog, SOS; Son Of Sevenless Homolog,SMO; Smoothened, Frizzled Class Receptor, TNF; Tumor Necrosis Factor, TRAIL; tumor necrosis factor-related apoptosis induced ligand, WNT; Wingless-Type MMTV Integration Site Family.*

An array of dietary phytochemicals including phenolic acids, flavonoids, triterpenes and other dietary phytochemicals were tested in cell- and membrane-based transport inhibition assays of ABCG2. The non-flavonoid phytochemicals berberine, celastrol, ellagic acid, limonin, oleanolic acid, sinapic acid and ursolic acid demonstrated significant inhibition of ABCG2-mediated transport. Chrysoeriol, laricitrin, myricetin 3',4',5'-trimethylether, pinocembrin, quercitrin, tamarixetin, tricetin and tricetin 3',4',5'-trimethylether were also identified as novel flavonoid ABCG2 inhibitors (81). Interestingly, cannabinoids have been shown to be effective inhibitors of ABCG2 with IC_{50} of 1.7 μM reported for tetrahydrocannabinol (82).

Tian *et al*., investigated the interaction between ABCG2 and several bisbenzylisoquinoline alkaloid compounds (83). Using the LLC-PK1/BCRP cell model, the authors showed that the alkaloid compounds liensinine and dauricine were substrates of ABCG2, corroborating their results from molecular docking analysis. On the basis of intracellular accumulation of these compounds and substrate interaction at ABCG2 sites of hotspot specificty, the authors concluded that ABCG2 could mediate the excretion of liensinine and dauricine. The ABCG2 antagonist action of these compounds could potentially be used in chemosensitizing CSCs to toxic action of various CTs.

Salinomycin

Salinomycin is a polyether ionophore antibiotic isolated from *Streptomyces albus*, that has been shown to kill CSCs in different types of human cancer, most likely by interfering with

ABC drug transporters, the WNT/β-catenin signaling pathway, and other CSC pathways. It is not clear by which mechanisms salinomycin eliminates CSCs, but it is important to note that salinomycin, in combination with cytotoxic drugs was much more effective in eradicating human cancer in mouse xenograft than CT drug alone (84). This reinforces the notion that efficient cancer therapy should target all cancer cell populations, including CSCs, more differentiated progenitors, and bulk tumor cells that may be achieved by combining CSC-targeting agents against new molecular and cellular targets with conventional cytotoxic modalities such as CT drugs and radiation.

Isothiocyanates. Cruciferous vegetables such as broccoli and sprouts contain isothiocyanates including sulforaphane, that are enzymatically hydrolyzed from glucosinolates (85). Dietary isothiocyanate sulforaphane was shown to alter phosphorylation of several kinases and their substrates including GSK3, JNK and Protein Kinase C (PKC) (86). Sulforaphane was also shown to target breast CSCs and was associated with reduction of AKT, phospho-GSK3β and β-catenin (87). Sulforaphane showed strong chemopreventative activity in challenges posed by chemically induced cancers in animal models (88). Kallifatidis *et al*., reported that sulforaphane could abrogate the resistance of pancreatic CSCs to tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) by interfering with TRAIL-activated NF-κB signaling (89). Hence, they concluded that combination of sulforaphane with TRAIL would be a promising strategy for targeting pancreatic CSCs. Sulforaphane has also been reported to down-regulate NF-κB function in prostate and colon cancer cells (90). Expression of WNT-9a was shown to be significantly suppressed in $Apc^{Min/+}$ mouse adenomas treated with sulforaphane (91).

Sulforaphane. Sulforaphane was shown to induce down-regulation of β-catenin in human cervical carcinoma HeLa and hepatocarcinoma HepG2 cells, although no direct effects on CSCs have been demonstrated to date (92). Sulforaphane has been reported to down-regulate AKT pathway in ovarian, prostate, and colorectal cancers and it was demonstrated that PI3K/AKT pathway regulates breast stem CSC by promoting β-catenin downstream events through phosphorylation of GSK3β (77). In studies, non-obese diabetic/severe combined immunodeficiency (NOD/SCID) mice inoculated with tumor cells derived from sulforaphane-treated primary xenografts failed to develop tumor re-growth up to 33 days, whereas control tumor cells quickly gave rise to large tumors (87). This was associated with down-regulation of WNT/β-catenin self-renewal pathway in sulforaphane-treated breast cancer cells.

Isoflavones. Consumption of dietary soy isoflavones including genistein has been shown to be associated with reduced risk of breast cancer in recent studies (93). The soy isoflavone genistein has been shown to have a potent antiproliferative effect on various types of cancer (94). Soy isoflavones were found to inhibit the phosphorylation of AKT and Forkhead Box O 3a (FOXO3a), enhance the expression of GSK3β, leading to increased phosphorylation of β-catenin in prostate cancer cells (95). Genistein was reported to attenuate β-catenin-mediated expression of WNT downstream target genes in mammary epithelial cells by up-regulating E-cadherin (96). Montales *et al*., showed repression of mammosphere formation of human breast cancer cells by soy isoflavone genistein and blueberry polyphenolic acids illustrating the potential of diet-mediated targeting of CSC/progenitor cells (97). Ning *et al*., investigated the activity of a genistein derivative and observed specific inhibition of ovarian CSCs mediated by down-regulation of *FOXM1* (98).

Polyphenols. Polyphenolic catechins including epigallocatechin-3-gallate (EGCG) found in green tea extracts have demonstrated chemopreventative activity against various types of cancers (99). EGCG has been shown to inhibit NF-κB activity, Mitogen-Activated Protein Kinase (MAPK) pathway, activator protein-1 (AP1) activity, and EGFR-mediated downstream signaling pathways, *etc*. (100). Several mechanisms of EGCG may be operative in WNT inhibition. EGCG was shown to block WNT signaling by stabilizing mRNA of WNT inhibitor HMG-box transcription factor 1 (*HBP1*), resulting in reduction of breast cancer cell proliferation and invasiveness (101). Other reports have shown EGCG to activate endogenous WNT inhibitor protein Secreted frizzled-related protein 1 (SFRP1) in hepatoblastomas (102). Adenomas isolated from EGCG-treated $Apc^{Min/+}$ mice, the benchmark transgenic model for recapitulating human colon cancer, showed inhibition of tumorigenesis, as evidenced by decreased nuclear import of β-catenin, lower pAKT levels and reduced adenoma size (103). EGCG was also shown to inhibit the chaperoning function of heat-shock protein 90 in pancreatic cancer cells, thereby down-regulating AKT signaling (104). EGCG was reported to negatively regulate NF-κB activity by inhibiting its ATP or Interleukin 1β (IL1β) activation (105). Shh expression and Hedgehog signaling pathway are still being evaluated as targets of EGCG, however, numerous reports have shown the ability of EGCG to specifically modulate CSCs in a variety of cancer types (106). Eid *et al*., investigated the cytotoxicity of various phytochemicals, including phenolics (EGCG and thymol), terpenoids (menthol, aromadendrene, β-sitosterol-O-glucoside, and β-carotene) and alkaloids (glaucine, harmine, and sanguinarine), alone or in combination with the cytotoxic monodesmosidic steroidal saponin digitonin in Caco-2, MCF-7, CEM/ADR5000, and CCRF-CEM cells (107). Digitonin was combined together with combinations of phenolics, terpenoids, and alkaloids and exhibited synergistic therapeutic effects even in MDR cells such as CEM/ADR5000 cells expressing high levels of ABCB1.

Saponin. Saponins are glycosides found in abundance in various plant species. Saponins from the roots of *Platycodon grandiflorum* suppressed Transforming Growth Factor β1 (TGFβ1)-induced epithelial-mesenchymal transition *via* repression of PI3K/AKT, ERK1/2 and SMAD2/3 pathway in human lung carcinoma A549 cells (35). SB365, a saponin D-derivative obtained from *Pulsatilla koreana* suppressed tumor sphere formation, reduced HIF1α and VEGF expression, and induced apoptosis of pancreatic cancer cells (108).

Quercetin. Quercetin is a polyphenol flavanoid found in various fruits, vegetables, leaves and grains. Wang *et al*., investigated the cooperative effects of administration of the querecetin and green tea in human prostate cancer xenografts in mice (109). Inhibition of tumor growth was correlated with effects of administration of the two compounds with numerous effects on important stem cell markers including ABCC1. Quantitative Real time-Polymerase Chain Reaction (qTR-PCR) analysis of catechol-*O*-methyltransferase and *ABCC1* gene expression revealed cooperative down-regulation of these genes by co-administration of querecetin/green tea.

Curcumin. Curcumin derived from the spice turmeric (*Curcuma longa*) has been reported to modulate multiple signaling pathways in a variety of cancer types. Curcumin blocked the pro-inflammatory transcription factor NF-κB *via* down-regulation of 26S-driven degradation of IκBα in Human Papilloma Virus (HPV)-associated cervical cancer cells (110). Esophageal squamous carcinoma is an aggressive cancer with poor prognosis due to the presence of CSCs (111). Almanaa *et al*., investigated the effects of curcumin on CSCs of human esophageal squamous carcinoma cells lines (112). ALDH1A1, $CD44^+$ and NF-κB were used to compare CSC sub-populations within original cell lines surviving up to 60 μM curcumin treatment. Curcumin-surviving cell lines showed significant loss in $ALDHA1^+$ and $CD44^+$ cell populations, indicating selective targeting of CSC population by the natural product. Furthermore, the tumor sphere-forming capability of YES-2 (human squamous carcinoma) cell lines surviving curcumin treatment was significantly lower than that of the untreated parental cell line.

Clearly, the ability of curcumin to target CSC populations within a tumor makes it an attractive candidate for combination therapy with established CTs in which tumor recurrence suggests ineffective eradication of CSC sub-populations. Yu *et al*., combined curcumin with either 5-fluorouracil or oxaliplatin, and observed a significant inhibition of CSC population which was confirmed by CSC markers such as CD44 and CD166 in colon cancer cell lines that are resistant to CT agents (113). Similarly, curcumin in combination with the CT agent dasatinib down-regulated ALDH, CD44, CD133 and CD166 markers at mRNA level in chemoresistant colon cancer (12).

Other polyphenols. Gingerols are found in abundance in ginger, and differ in their chemical structure by the length of unbranched alkyl chains. 6-Gingerol has been purported to exert cancer chemopreventative effects by influencing various steps of the metastatic process (114). MDA-MB-231 cells treated with 6-gingerol showed reduction in matrix metalloproteases MMP2 and MMP9 and pointed towards favorable response to the drug in processes involved in cell adhesion, migration, invasion and proliferation (115). Growth arrest and apoptosis of human colorectal cancer cells treated with 6-gingerol, was also shown to occur by multiple mechanisms including protein degradation as well as β-catenin, PKC and GSK3β pathways (116). Tests of 6-gingerol on CSC sub-populations appear warranted. Shogaol (6-shogaol), is a constituent of ginger. A derivative of shogaol, 3-Ph-3-SG, was shown to inhibit Phorbol 12-myristate 13-acetate (PMA)-activated MMP9 expression in MDA-MB-231 and MCF-7 breast carcinoma cells (117). Invasion was suppressed by exertion of cytoprotective effects through modulation of NF-κB and Nuclear respiratory Factor 2 - Kelch-like ECH-associated protein 1 (NRF2-KEAP1) signaling pathways.

The terpenoid phenolic aldehyde, gossypol, is generally isolated as a racemic mixture from cottonseed plant (*Gossypium*). The tumor-inhibitory properties of gossypol in CSC-relevant pathways have been ascribed to blocking of the anti-apoptotic functions of BCL-2 and BCL-xL, (118), p53 induction (119) and even VEGF angiogenesis (120), although it appears its mechanism of action is more consistent with its inhibition of dehydrogenase enzymes, including various ALDH isozymes (51). Gossypol acts as a noncompetitive inhibitor of ALDH and was shown to be more selective for ALDH3 than ALDH1 and ALDH2 isozymes, perhaps reflecting on the paucity of its screening as a prospective CSC inhibitor. (121). Sabutoclax, a selective MCL1 antagonist derived from gossypol inhibited tumorigenesis in transgenic mouse and human xenograft of prostate cancer (122).

Psoralidin, a natural phenolic compound found in the seeds of *Psoralea corylifolia*, was shown to induce growth arrest of $ALDH^+$ breast CSCs derived from MDA-MB-231 by down-regulation of *Notch1* (123).

Vinca alkaloids. Vinorelbine, a potent vinca alkaloid, was suggested as a possible treatment against breast CSCs (124). A screen of colorectal carcinomas obtained from patients treated with vinorelbine, however, indicated remission of tumors and relapse of cancer cells on the basis of high proliferative index, and overexpression of CSC markers NANOG, BM1, CD44, CD133 and Death receptor 5 (DR5). It was suggested that the Notch signaling pathway and mTOR signaling may be responsible for these effects (125).

Sesquiterpene lactones. Parthenolide is a sesquiterpene lactone of the germacranolide class which occurs naturally in the plant

feverfew (*Tanacetum parthenium*). Guzman *et al*., investigated activity of parthenolide against CSCs derived from AML and CML (126). Parthenolide induced significant apoptosis in primary human AML cells and blast crisis CML cells while sparing normal hematopoietic cells. In NOD/SCID mice, parthenolide exhibited preferential targeting of AML progenitor and stem cell populations when compared to the established chemoptherapeutic drug, cytosine arabinoside. Inhibition of NF-κB, proapoptotic activation of p53, and increased reactive oxygen species were factors cited by the authors in parthenolides activity against these CSCs. (−)-Galiellalactone is a fungal metabolite that can be isolated from ascomycetes *Galiella rufa* strain. Hellsten *et al*., showed that galiellalactone inhibited CSC-like $ALDH^+$ DU145 and LNCaP prostate cancer cell proliferation and tumorigenicity in mouse xenografts by targeting JAK/STAT phosphorylation of STAT3 (127).

Polyynes

Falcarinol and falcarindiol are polyacetylenes derived from carrot, parsley and devil's club (*Oplopanax horridus*) which is related to ginseng. Yoshida *et al*., demonstrated that falcarindiol can inhibit GSK3β in an ATP noncompetitive manner (128). Falcarinol derivatives were shown by Tan *et al*., to be potent inhibitors of breast cancer resistance protein (ABCG2) (81). The evaluation of these compounds against CSCs represents an intriguing future direction for CSC research.

Conclusion and Future Perspectives

Conventional therapeutics including chemotherapy and radiation therapy have demonstrated efficacy against many differentiated tumor cell types, but exhibit poor performance against CSC-specific targets, leading to tumor regrowth and metastasis. Many NPs, including those found in common foodstuffs have demonstrated ability to modulate pathways responsible for CSC function and inhibition. As knowledge of molecular biology and properties of CSCs is gleaned for various tumor types, more NP inhibitors of CSCs may be identified and tested in combination with each other and in formulations with conventional CT drugs to form more potent therapeutic treatment strategies than those currently available.

Conflicts of Interest

The Authors indicate no potential conflict of interest.

Acknowledgements

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