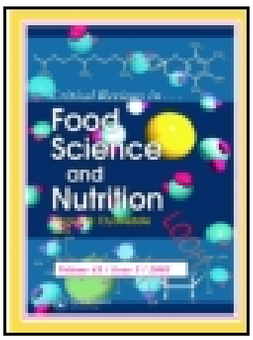

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Emerging Importance of Dietary Phytochemicals in Fight against Cancer: Role in Targeting Cancer Stem Cells

AMIT KUMAR SINGH[1], NEELESH SHARMA[2], MRINMOY GHOSH[1], YANG HO PARK[3] and DONG KEE JEONG[1,*]

[1]Laboratory of Animal Genetic Engineering and Stem Cell Biology, Department of Animal Biotechnology, Faculty of Biotechnology, Jeju National University, Jeju, Republic of Korea

[2]Division of Veterinary Medicine, Faculty of Veterinary Science and Animal Husbandry, Sher-e-Kashmir University of Agricultural Sciences and Technology, R.S. Pura, Jammu, India

[3]BRM Institute, Seoul, Republic of Korea

[*]Address correspondence to Prof. Dong Kee Jeong, Department of Animal Biotechnology, Faculty of Biotechnology, Jeju National University, Ara-1 Dong, Jeju-city, Jeju-Do 690-756, South Korea, Email: newdkjeong@gmail.com; dkjeong@jejunu.ac.kr, Tel: +82-64-754-3331; Fax: +82-64-725-2403

Recent years have seen an unpretending increase in research using dietary phytochemicals for targeting cancer and cancer stem cells (CSCs) due to the limited efficacy of conventional chemotherapy and radiotherapy and numerous associated side effects. A large number of dietary phytochemicals using traditional recommendation and experimental approaches have been demonstrated to have anti-proliferative, anti-metastatic, reactive oxygen species (ROS) inducing, anti-angiogenic, pro-apoptotic effects and efficacy in targeting cellular molecules and pathways implicated in malignancy. Researchers have shown the knack of phytochemicals in interfering with the CSCs self-renewal process. Thus, dietary phytochemicals can play a significant role in the cancer therapy owing to the plethora of targets without toxicity. In this review, we have

discussed about the basic knowledge of CSCs, their identification, characterization, mechanism of self-renewal pathways (Wnt/β-catenin, Hedgehog and Notch), features that help in the survival of CSCs and use of phytochemicals to replace chemotherapy. Applications of phytochemicals including curcumin, epigallocatechin-3-gallate (EGCG), resveratrol, lycopene, and sulforaphane for their effect on targeting cancers and in particular CSCs along with their molecular mechanisms responsible for pharmacological action are also discussed.

Keywords

Dietary Phytochemicals, cancer stem cells, therapeutic agents, molecular mechanisms, multi-targets

INTRODUCTION

Cancer is a disease caused by uncontrolled growth of cells in a specific part of the body and may be either benign or malignant. Malignant tumors have the potential to invade or spread into the surrounding tissue environment via the circulatory or lymphatic system (metastasis). Despite recent advances in understanding disease biology and drug discovery, it is often fatal; hence, global efforts are persistently being carried for designing effective drugs and therapeutic strategies for disease management. Cancer accounts for nearly 13% of total death worldwide with approximately 14.1 million new cases. As per World Health Organization (WHO) reports, 8.2 million cancer-related death was reported in 2012 and estimates are there that it may increase by 21.7 million in next 2 decades that highlight the urgency for drug discovery for disease management (WHO, 2015).

Earlier drug development strategies against cancers were based on the somatic mutation theory, where the transformation of normal somatic cell into malignant cell is the result of chronological genetic mutations and alteration in gene regulation pattern (Hahn *et al*., 1999; Hanahan and Weinberg, 2000). Cancer research has made a remarkable progress over the last decade and clarified our understanding of these hallmark capabilities and also led to modifications. A review by Hanahan and Weinberg (2011) has described the hallmark of cancer development and included sustained proliferative signaling, growth suppressors evasion, invasion and metastasis, cell death resistance, replicative immortality, angiogenesis induction, genomic instability and mutation, tumor promoting inflammation, cellular energetics deregulation and avoiding immune obliteration. These hallmarks are functional within the context of the tumor microenvironment. The second archetype, which emerged more recently, is

the cancer stem cells (CSCs) theory of oncogenesis, which hypothesize that transformation of a somatic cell into CSCs is the accumulative result of genomic mutations and epigenomic alterations that transform the somatic cells and result in its "germinalization" (Erenpreisa *et al*., 2015). It is also plausible that CSCs may arise from tissue-specific stem cells (SCs) by mutation of genes that make the stem cells cancerous (Clarke *et al*., 2006). The process of tumorigenesis is driven by CSCs by asymmetric cell division and give rise to one cell of equivalent potency i.e. CSC, another may be of the same potency or stimulated to further differentiation and it makes up the bulk of the tumor (Vinnitsky, 2014). CSCs are anticipated to be responsible for tumor development, initiation of invasion and metastasis as well as recurrence (Liao *et al*., 2014).

The First evidence about CSCs came from a seminal work in 1994 when a subpopulation of cells with $CD34^{(+)}/CD38^{(-)}$ phenotype were demonstrated to have the capacity to induce leukemia in immunocompromised mouse model and possessed the proliferative and differentiation capacity and the potential for self-renewal (Bonnet and Dick, 1997; Lapidot *et al.,* 1994). This incited various researchers to take experiments on demonstration of CSCs from various other malignancies like colon cancer, breast cancer, prostate cancer, pancreatic cancer and hepatic cancer including osteosarcoma (Dick, 2008; Hermann *et al.,* 2010; Magee *et al.,* 2012; Reya *et al.,* 2001; Ward and Dirks, 2007). Al Hajji *et al* (2003) first reported the existence of CSCs in solid tumor and showed that the cells that are $CD44^{high}CD24^{low}$ possessed tumor-initiating capacity. Malignant tissues are now no longer viewed as homogeneous masses of proliferating cells having indistinguishable genetic alterations, but more as a heterogeneous tissue that contains a hierarchy of cells, perhaps originating from a single CSC.

The concept of stem cell niche came from the elegant work of Schofield (1978) on hematopoietic cells. Referring to the similarity between normal stem cells and CSCs, it is good to assume that CSC niche exists and this concept has been supported by various studies in different cancer models by several search groups (Calabrese *et al.,* 2007; Krishnamurthy *et al.,* 2010; Lu *et al.,* 2014; Mishra *et al.,* 2008; Shinagawa *et al.,* 2010). Tumor niche provides the regulated environment that controls proliferative capacity, stemness and resistance to apoptosis and its architecture are quite complex. Niche is derived from mesenchymal and immune cells, soluble factors, cytokines, vascular network and extracellular matrix component (Borovski *et al.,* 2011). Tumorigenicity is not inclusive of the biology of tumor cells, but depends on rather the dynamic interaction between tumor cells and nonmalignant cells that make up tumor environment. Evidences suggest that quiescent cells present within a solid tumor maintain a stable functioning tumor despite external perturbations by therapy. Differentiated cells actively promoted proliferation of their clonemates in accomplishing growth-fostering functions and included angiogenesis, immunoediting and construction of an advantageous microenvironment to shelter the CSCs (Grunewald *et al.,* 2011). CSCs like other normal stem cells depend on the permissive environment to retain their intrinsic property of self-renew and differentiation while staying itself in an undifferentiated state. CSC niche provides an environment by sheltering CSCs from diverse genotoxic insults and contributes to chemoresistance (Borovski *et al.,* 2011). CSCs have an excellent DNA repair capacity and also express higher levels of drug transporters that contribute to theoretical immortality to current cancer chemotherapy.

Current treatment strategies for cancer include chemotherapy, radiotherapy and surgery and even with advanced medical interventions, a large number of patients suffer from poor

outcome. The present chemotherapy includes use of antimetabolite (e.g. methotrexate), antitubulin agents (taxanes), DNA-interactive agents (cisplatin, doxorubicin), hormone and molecular targeting agents (Nussbaumer *et al.*, 2011). However, such treatment strategies are associated with several unwarranted side effects such as hair loss, gastrointestinal lesion, bone marrow suppression, neurologic dysfunction, drug resistance, etc. (Dropcho, 2011; Monsuez *et al.*, 2010). The current therapeutic strategy focuses on highly proliferative differentiated cells forming the bulk of the tumor but not CSCs that are in quiescent stages and may account for treatment failures (Boman and Wicha, 2008). It has prompted to look for new therapeutics with less or minimal side effects. A new paradigm shift in treatment strategy is to target CSCs together with the proliferating bulk of the tumor cells, blocking their ability to self-renew and generate multilineage differentiation (Ma and Allan, 2011).

Analysis of epidemiological data highlights that use of fruits and vegetables reduces the incidence of cancer (Campbell *et al.*, 1998; Carroll *et al.*, 1986; Lanou and Svenson, 2010). Phytochemicals have attracted researchers throughout the world for a possible therapeutic purpose because of minimal toxicity and maximum efficacy **(Fig.1)**. Screening of phytochemicals against malignant cells displayed better efficacy both in *in vitro* and *in vivo* experiments in term of inhibiting cell proliferation, angiogenesis and apoptosis induction (Hajzadeh, 2006; Mortazavian *et al.*, 2012; Sadeghnia *et al.*, 2014; Veeraraghavan *et al.*, 2011; Weng and Yen, 2012). Some of the plants-derived compounds have already entered in the market. For instance, Taxol analogues, Vinca alkaloids (vincristine, vinblastine) and Podophyllotoxin analogues have played an important role in the treatment of cancer patients (Lucas *et al.*, 2010; Nobili *et al.*, 2009). In this review, we have discussed in detail about the

cancer stem cell biology and the potential application of phytochemicals for targeting CSCs along with their mechanisms of action.

SUBSTANTIATION FOR CANCER STEMS CELLS

Detection of CSCs in many cancer types has been uprising by identification of various surface antigens present in tissue-specific cancer stem cells **(Table 1)**. However, the identification of CSCs based on surface marker expression is inefficient and must be accompanied by other functional assays such as the sphere-forming assay in non-adherent medium, replating assays, Hoechst dye exclusion ability because of over-expression of efflux transporters, detection of enzymatic activity of Aldehyde dehydrogenase (ALDH), transplantation assays and measurement of the expression of specific CSC genes to provide convincing evidence for the existence of CSCs. Sphere forming assay utilizes the property of stem cell growth in serum-free, non-adherent condition and occurs at the rate ranging from 0.1 to 1% depending on the number of cancer stem/progenitor cell population. Hoechst dye exclusion is an important technique for the purification, recognition, fortification of stem cells and early progenitors in tissue samples. This method exploits the cell property of passive uptake of dye when alive, where stem cells can be differentiated from other live cells by their ability to pump out Hoechst dye via the ATP-Binding Cassette (ABC) transporters allowing the differentiation of CSCs from other cells by quantifying and selecting less fluorescent cells. Aldehyde dehydrogenases (ALDHs) enzymes are present in the cytoplasm, involved in detoxifying a wide variety of aldehydes to their corresponding weak carboxylic acids (Vasiliou *et al.*, 2000). ALDH is used as a marker for the identification and isolation of CSCs because of its role in normal as well as cancer stem cell biology. Determination of ALDH activity helped in the identification of

CSCs in a number of carcinomas, including breast, liver, colon and leukemia **(Table 1)**. CSCs have the unique property of self-renews and differentiation that can be utilized as a gold standard assay for differentiation of normal stem cells from CSCs. It involves transplantation of cells in immunocompromised mice followed by monitoring for tumor development at various time points. It is further examined by isolation of cells from xenograft tumor and its implantation into another immunocompromised mouse shows self-renewal and tumor formation capacity.

CSCS SELFRENEWAL: MOLECULAR INSIGHT

Numerous genes and signaling pathways have been shown to have important regulatory functions for the both normal and cancer stem cells. However, aberrant regulation of these pathways leads to cancer resulting in abnormal transformation and possibly tumorigenesis. Notch, Hedgehog (Hh) and Wnt/β -catenin pathways have been shown to be involved in the regulation of the self-renewal process of both SCs and CSCs (Liu *et al.*, 2005). Hedgehog (Hh), a glycoprotein, is involved in pro-survival pathways, Notch, a trans-membrane receptor, is involved in the self-renewal processes and Wnt/β-catenin protein is involved in the self-renewal pathways.

The Notch pathway is an intracellular communication system between a transmembrane receptor and ligand that transduces cell fate regulatory signals. Notch receptors have four isoforms that function independently and even have a contrary effect and contributes to maintaining either stem cell characteristics or lead to tissue-specific differentiation (Radtke and Raj, 2003). Notch pathway contribution in different type of cancers has been elucidated and in Non-Small Cell Lung Cancer (NSCLC), malignant cell survival is promoted by inhibiting proapoptotic Bim and inducing antiapoptotic survivin through Notch3 upregulation

(Osanyingbemi-Obidi *et al.,* 2011). Activation of Notch1/2 resulted in tumor suppressive effect in NSCLC and chronic myelomonocytic leukemia (CML) cell lines (Liu *et al.,* 2013). The Notch pathway has also been found to be active in melanoma (Gajewski, 2011). Notch1 appears to promote disease progression and growth of melanocytes under hypoxic condition (Bedogni *et al.,* 2008).

The Hh signaling pathway regulates vertebrate embryonic development and also contributes in stem cell maintenance, cell differentiation, and proliferation regulation. It was initially identified in Drosophila and plays an important role in segmental patterning during embryonic development. It also regulates the proliferation, migration and differentiation of target cells in a spatial, temporal, and concentration dependent manner (Rubin and de Sauvage, 2006). In normal condition, it remains under inhibition and signaling cascade is initiated by the binding of ligand to patched-1 protein (PTCH-1), which remains bound with seven-transmembrane-span receptor-like protein, SMO in the absence of ligand (Taipale *et al.,* 2002). The SMO activation process is observed in a variety of cancer types such as lung, breast, brain, gastrointestinal and prostate cancer (Berman *et al.,* 2003; Clement *et al.,* 2007; Karhadkar *et al.,* 2004; Kubo *et al.,* 2004; Sicklick *et al.,* 2006). Hh signaling constitutive activation leads to malignancy in medulloblastoma and basal cell carcinoma (BCC) (Tostar *et al.,* 2006). Lo *et al* (2014) reported aberrant Hh signaling in the pathogenesis of osteosarcoma. Watkins *et al* (2003) revealed that NSCLC cells were dependent on Hh signaling for their malignant behavior. Presently, the mechanism of Hh signaling is not completely understood; nevertheless, it is clear is that aberrant Hh signaling does result in tumor growth, proliferation, aggression and metastasis.

The Wnt/β-catenin pathway initiates a signaling cascade critical in both normal embryonic development and throughout the life of an organism and is one of the most important target candidates in malignancy (Lenz and Kahn, 2014). It has been confirmed that activation of the Wnt pathway leads to inhibition of GSK-3β, thereby, blocking β-catenin phosphorylation and promotes its translocation to the nucleus. It leads to the activation of T cell factor-lymphoid enhancer factor (TCF-LEF) and increases the self-renewal and proliferation of CSCs (Brittan and Wright, 2002; Reya *et al.,* 2003). Experiments in mice expressing constitutively activated β-catenin demonstrated highly proliferative malignancy (Zito *et al.,* 2014).

Although, there is a large gap in our understanding regarding the extremely multifarious network of mechanisms that regulate CSC renewal and carcinogenesis, studies conducted in various labs have shown that the stemness factors, e.g., NANOG, SOX2, OCT4, LIN28, c-Myc and Kruppel-like factor 4 (KLF4) regulates the tumorigenic potential of these cells and it can transform normal fibrocytes into malignant cells by their expression (Shi *et al.,* 2008b).

BATTLE WAGED FOR TARGETING CSCS AND THEIR OUTCOME: CURRENT SCENARIO

Conventional anticancer strategies have shown limited survival rate when used in the advance stage of cancer because their prime target is rapidly dividing cells. However, CSCs hypothesis assumes as a source of regeneration and metastasis, and anticancer agents may not eradicate them because of its rare dividing tendency. CSCs also display enhanced mechanism of DNA damage repair, amplified antiapoptotic activity, enhanced xenobiotic efflux, and skewed production of certain cytokines (Cojoc *et al.,* 2015). It would be fascinating to develop new therapeutic strategies targeting CSCs with target specificity using either developing monoclonal

antibodies specific for surface antigen, self-renewal pathway or by induction of differentiation and modulating CSC microenvironment.

Signaling pathways such as Hh, Wnt/β-catenin and Notch pathways involved in differentiation of normal stem cells offer an attractive approach to target CSCs (Bouras *et al.,* 2008; Brennan and Brown, 2004; Liu *et al.,* 2006). The Wnt/β-catenin pathway signaling dysregulation has been shown to cause the majority of cancer cases (Brittan and Wright, 2002). A lot of efforts have been made to identify small molecules capable of disrupting aberrant Wnt/β -catenin pathway responses and monoclonal antibodies and siRNA against Wnt1/2 have been evaluated in patients with improved outcome (Deonarain *et al.,* 2009; Teng *et al.,* 2010). Nonsteroidal anti-inflammatory drugs (NSAID) such as Aspirin and Sulindac demonstrated inhibition of Wnt signaling by inhibiting COX2 (Gurpinar *et al.,* 2014). Compound XAV939 affecting the interaction between TCF/β-catenin via stimulating β-catenin degradation has entered into the preclinical trial (Huang *et al.,* 2009). Vitamins A and D and their derivatives via their ability to interfere with β-catenin/TCF interactions allows E-cadherin to reposition β-catenin to the membrane (Mulholland *et al.*, 2005). Notwithstanding this advancement, targeting the Wnt pathway is still in its infancy and none of the therapeutic agents has yet been approved for clinical use and still are in the stage of clinical trial (Kahn, 2014).

Blockade of Notch signaling by γ-secretase inhibitors depleted $CD133^+$ in glioblastoma and promoted increased responsiveness to radiation (Fan *et al.,* 2010). The delta-like ligand 4 (DLL4) participates in CSC self-renewal and vascular development by binding with any of the 4 Notch receptors has emerged as one of the attractive target for anticancer therapy (Gurney and Hoey, 2011). Demcizumab (anti-DLL4, OMP-21M18), is a monoclonal antibody that selectively

targets Delta-like ligand 4 (DLL4), is currently under phase 2 clinical trial against pancreatic cancer and NSCLC and demonstrated good activity (Kwiatkowska-Borowczyk *et al.,* 2015). Vantictumab, a monoclonal antibody against the Frizzled receptors 1, 2, 5, 7 and 8 in combination with standard chemotherapy displayed strong anti-tumor activity (Gurney *et al.,* 2012). Evidence have emerged that combining Notch1 inhibitor enhanced drug resistant breast cancer cell line response to current chemotherapy and radiotherapy (Cho *et al.,* 2011; Zang *et al.,* 2010). However, the utility of Notch1 antibody-based targeting in isolation is questionable because of the redundancy of Notch receptor, ligands and questionable patient safety profile (Yan *et al.,* 2010).

Another important target that is crucial in regulating CSC self-renewal mechanism is inhibition of Hedgehog signaling (Hh) and is gaining much attention in the last few years. Aberrant signaling is observed in various neoplasms such as BCC, medulloblastoma, osteosarcoma resulting in increased cell proliferation and tumor formation and is gathering interest among researchers for developing inhibitors as anti-cancer target (Tostar *et al.,* 2006). The first clue that Hh pathway can be targeted came from the work of Chen *et al.* in 2002, where they evaluated the efficacy of cyclopamine, a plant derived compound, as an antagonist for SMO transfected mouse cell line (Chen *et al.,* 2002). The experiments revealed that cyclopamine targets CSCs in CML and impaired the growth of imatinib-resistant mouse and human CML cells (Chen *et al.,* 2002; Zhao *et al.,* 2009). In phase 1 clinical trial involving advanced BCC and medulloblastoma patients, one Hh inhibitor, Vismodegib, a cyclopamine derivative, was found to have anti-tumor activity and acceptable safety profile and has been approved by the United

States of America food and drug administration (USA FDA) (Abidi, 2014). However, long-term studies are warranted to monitor its safety and efficacy.

Gli (glioma-associated oncogene homologs) transcription factors are a critical mediator of the Hh signaling pathway and their atypical activation may induce tumor cell proliferation and invasion. Gli inhibitors are therefore being considered as a new therapeutic target for malignancy. Arsenic trioxide (ATO) is an FDA-approved drug used for the treatment of patients with acute promyelocytic leukemia (APL) (Mathews *et al.*, 2011). ATO unswervingly binds to Gli1 and Gli2 and inhibit its transcriptional activity and thereby downregulates the expression of endogenous Gli target genes. Gli inhibitors GANT 61(Gli activators antagonist) modifies Gli 1 and Gli 2 and prevent them from binding to the DNA promoter (Lauth *et al.*, 2007). As Gli 2 is intricately implicated in bone development, possible side-effect of antagonist may include bone defects.

The tumor microenvironment provides a niche to nurse and protects CSCs from drug-induced apoptosis. Therefore, therapies targeting the microenvironment offers an alternative pathway to eradicate CSCs. CSCs of B-cell malignancy resides in the bone marrow via interaction with C-X-C motif chemokine 12 (CXCL 12) and C-X-C chemokine receptor type 4 (CXCR 4). CXCR4 antagonists such as Plerixafor (AMD3100) and T14003 analogs, which are currently under clinical trial for leukemia, breaks adhesive tumor-stroma interaction and induce leukemia cell migration away from the bone marrow stromal microenvironment and enhance cells' susceptibility to cytotoxic drugs (Burger and Peled, 2009).

Tumor angiogenesis has been reported with CSCs survival and growth and is mediated by vascular endothelial growth factor (VEGF). Recent *in vivo* experiment in a mouse model of

glioblastoma demonstrated combined VEGF and CXCR4 antagonism using Avastin (VEGF inhibitor) and POL5551 (CXCR4 inhibitor) and enhanced survival rate (Barone *et al.*, 2014).

Another approach to targeting CSCs is based on the inhibition of the mammalian target of rapamycin (mTOR). The mTOR is considered as a key signaling molecule that drives uncontrolled glioblastoma tumor proliferation and also seems to be critical for breast CSC survival (Zhou *et al.,* 2007). mTOR inhibitor, rapamycin, depleted leukemia-CSCs without affecting normal stem cells (Yilmaz *et al.*, 2006).

However, none of such anti-CSC agents demonstrated complete tumor eradication and were also not devoid of side-effects; thereby substantiate the need for alternative treatment strategies to eradicate cancer.

PHYTOCHEMICALS: A MULTITARGETED APPROACH FOR CANCER THERAPY

Natural products (phytochemicals) have attracted people across the world for centuries for numerous applications including curing disease. Studies revealed that inclusion of certain ingredients or items in the diet leads to reducing cancer incidence in the certain part of the world. e.g. Mediterranean peoples have a low incidence of cancer because of a diet rich in olive oil and tomato (Schwingshackl and Hoffmann, 2014). Adverse side effects with current chemotherapy have forced researchers to develop efficacious and safe options for treating malignancy. Ancient literature and epidemiological studies led to focus attention on phytochemicals because being natural, they do have minimal side effects and are easily acceptable. *In vitro* and *in vivo* studies carried out in animals using phytochemicals have shown to interfere in signal transduction pathways of malignant cells (**Fig. 2**), and thus inhibiting cell proliferation, differentiation, angiogenesis and anti-apoptosis **(Fig. 3). S**ome of these compounds have also shown

effectiveness in clinical trials (Banerjee *et al.,* 2011; Dashwood and Ho, 2007; El-Alfy *et al.,* 2011; Epstein *et al.,* 2010; Yang *et al.,* 2007). Different laboratories across the world, including ours, have revealed the therapeutic efficacy of phytochemicals in the treatment of cancer and particular targeting of CSCs (Mongre *et al.,* 2015a; Mongre *et al.,* 2015b; Sharma *et al.,* 2014). Below, we discuss the effects of phytochemicals in targeting different pathways of malignant cells with special attention to CSCs in order to regress the cancer finally from its origin **(Table 2)**.

Cell proliferation and cell cycle arrest

CSCs hypothesis and subsequent isolation of CSCs from tumors have demonstrated that CSCs have the capacity of propagation and metastasis and aberrant regulation of various signaling pathways is responsible for malignancy. The phytochemicals that target various signaling events such Hh, Wnt, PI3K/Akt and Notch can be the useful therapeutic strategy in cancer treatment.

Atypical activation of Nuclear factor-kappa-B (NF-κB) and Activator protein-1 (AP-1) pathways provide protection against apoptosis and encourage proliferation in malignant cells (O'Gorman and Cotter, 2001). Phytochemicals that promote apoptosis induction and block cell proliferation and cell cycle progression are attractive drug candidates for cancer prevention and treatment. *In vitro* and *in vivo* studies in cancer model using phytochemicals have demonstrated upregulation of proapoptotic genes such as Bax, cytochrome c, activation of caspase cascade and poly (ADP-Ribose) polymerase (PARP) cleavage (Burz *et al.,* 2009; Neergheen *et al.,* 2010; Tan *et al.,* 2009). Curcumin (yellow pigment found in turmeric), epigallocatechin-3-gallate (EGCG) (the major polyphenol in green tea) and lycopene (present in tomato) were found to induce

apoptosis through p53-dependent Bax induction and inhibited cell cycle progression by upregulating p21waf1/Cip1 and p27Kip1 CDK inhibitors (Goel *et al.,* 2008; Khan and Mukhtar, 2008; Meeran and Katiyar, 2008). Studies in a mouse model of skin carcinogenesis demonstrated inhibitory effect of curcumin and gingerol (phenolic substance present in ginger) on tumor progression (Kim *et al.,* 2004; Limtrakul *et al.,* 1997). Curcumin has been reported to modulate miRNA expression profile in breast cancer cell line and induced apoptosis by reducing Bcl-2 expression (Kronski *et al.,* 2014). It also targeted breast CSCs without affecting normal stem cells (Charpentier *et al.,* 2014).

Isothiocyanates have shown to reduce the incidence of various cancers following dietary intake and mechanism has been ascribed to increased apoptosis, cell cycle arrest, inhibition of epithelial to mesenchymal transition (EMT), CSC self-renewal and signaling pathways respectively (Singh and Singh, 2012). Capsaicin (found in hot pepper) induced apoptosis in Jurkat cells through generation of reactive oxygen species (ROS) and rapid activation of c-Jun-NH2-kinase (JNK) pathway (Macho *et al.,* 2003). It inhibited constitutive as well as induced activation of NF-κB in human malignant melanoma cells (Han *et al.,* 2001). Curcumin, EGCG and resveratrol (found in grapes, berries, and peanuts) have been recently shown to inhibit Wnt signaling and targets self-renewal potential of CSCs (Jaiswal *et al.,* 2002; Kakarala *et al.,* 2010; Park *et al.,* 2014). Curcumin and resveratrol also effectively inhibited Notch signaling pathway governing self-renewal of colorectal CSCs, induced CSCs apoptosis and enhanced radio-sensitivity (Miyamoto and Rosenberg, 2011). A study in rat C6 glioma cell line demonstrated inhibition of side population (SP) phenotype by curcumin while another finding recognized the suppressive effect of curcumin and piperine on breast CSCs growth (Fong *et al.,* 2010; Kakarala

et al., 2010). Curcumin decreased β-catenin/TCF transcription activity in gastric, colon and intestinal cancer cell lines and also targeted breast stem/progenitor cells (Park *et al.*, 2005; Shakibaei *et al.*, 2013).

Sulforaphane (SF), obtained from broccoli, has been shown to be efficient in targeting CSCs by modulation of signaling pathways including NF-κB, Hh, Wnt/β-catenin and also EMT (Li and Zhang, 2013). SF was recently described to eliminate pancreatic CSCs by down-regulation of NF-κB activity without inducing toxic side effects (Rausch *et al.*, 2010). The phenomenon has also been reported in prostate and colon cancer cells (Suppipat *et al.*, 2012). SF in combination with Sorafenib (SO) exterminated SO-induced NF-κB in pancreatic CSCs (Rausch *et al.*, 2010). Combination therapy in mouse model demonstrated reduced tumor size in a synergistic manner by induction of apoptosis, proliferation and angiogenesis inhibition and also attenuated SO-induced expression of proteins involved in EMT. SF was effective in targeting breast cancer stem/progenitor cells *in vitro* and *in vivo* at lower concentrations (0.5- 5 μM) by downregulating Wnt/β-catenin self-renewal pathway (Li *et al.*, 2010). A study reported the activity of SF in down-regulating PI3K-Akt pathway in colorectal, ovarian and prostate cancers (Shankar *et al.*, 2008).

β-Carotene has been identified to inhibit the growth of CSCs and induced the differentiation of neuroblastoma cells (Lee *et al.*, 2013). It also decreased the self-renewal characteristics of CSCs, thereby preventing recurrence and metastasis. Genistein (a prominent isoflavone) inhibited cell growth and induced apoptosis by inhibiting the Notch signaling pathway. Soy isoflavone, genistein, and blueberry polyphenolic acids repressed mammosphere formation of breast cancer cells and Ginsenoside F2 induced apoptosis in breast CSCs by

promoting autophagy via phosphorylation of p53 (Mai *et al.,* 2012). NV-128 is an isoflavone derivative that targets mitochondria of $CD44^+$/$MyD88^+$ ovarian CSCs and induced apoptosis by two independent pathways: the AMPKα1 pathway that causes mTOR inhibition and loss of mitochondrial membrane potential via mitochondrial MAP/ERK pathway (Alvero *et al.,* 2011). Broussoflavonol B, a chemical purified from the bark of the Paper Mulberry tree reduced estrogen receptor (ER)-α36 expression and inhibited growth of ER-negative breast cancer stem-like cells and induced apoptotic cell death (Guo *et al.,* 2013). Polyphenolic compound, resveratrol was found to inhibit the expansion of breast CSCs and persuaded apoptosis through upregulation of death-associated protein kinase 2 (DAPK2) and BCL2/adenovirus E1B 19 kDa interacting protein 3(BNIP3) and downregulation of fatty acid synthetase (FAS). Furthermore, morusin, the main flavonoid present in the *Morus nigra* root barks, induced apoptosis of cervical CSCs by Bcl-2 and NF-κB/p65 pathway attenuation and dose-dependent upregulation of Bax and caspase-3 (Wang *et al.,* 2013b).

Phytochemical extract (BRM270) demonstrated *in vitro* and *in vivo* efficacy against osteosarcoma stem-like cancer initiating cells (SLCICs) by inhibiting cyclin-dependent cell division kinase-6 (Cdk6) and NF-κB pathway and promoted programmed cell death (Mongre et al., 2015a). *In silico* studies by Ghosh *et al* reported high binding affinity of Lipocalin 2 (LCN2) with MMP9, which plays a vital role in tumor growth and metastasis. BRM270 exhibited inhibition of LCN2 induced EMT process in $CD133^+$-A549-Tumor initiating cancer stem-like cells (TICSCs) xenografts by inhibiting NF- κB pathway (Ghosh *et al.,* 2015; Mongre *et al.,* 2015b). Salinomycin, a polyether antibiotic, widely used as an anticoccidial drug was recently shown to act as a specific inhibitor of CSCs by targeting P-glycoprotein (P-gp170) responsible

for multidrug resistance through induction of conformational change in ATP transporter protein (Riccioni *et al.,* 2010). Salinomycin elicited a dose-dependent inhibition of cell growth in CEM and A2780 ovarian carcinoma cells and restored vinblastine sensitivity in vinblastine-resistant cells. It also demonstrated diminished stem cell markers (OCT-4, NANOG and SOX2) expression and self-renewal/proliferation capacity in the lung cancer cell line. (Hu and Fu, 2012).

Angiogenesis inhibition

Angiogenesis plays a key part in tumor growth, progression and metastasis, and its suppression offer an attractive strategy for cancer treatment. Researchers have shown that VEGF promote breast and lung CSCs self-renewal via VEGF receptor-2 mediated upregulation of Myc and SOX2. Various phytochemicals contribute to inhibition of angiogenesis by interfering various pathways. Curcumin inhibits epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2 and VEGFR-3) and Wnt Signaling (Sung *et al.,* 2012). Increased Interleukin-1β, IL-6 and IL-8 concentration have been found in multiple cancers and promote chemoresistance, angiogenesis and invasion. They also promote the conversion of normal cancer cells to CSCs in recognized breast and prostate cancer cell line. Experiments demonstrated that curcumin inhibited Interleukin release from colon, head and neck squamous cell carcinoma and human chondrosarcoma cell lines, thus inhibiting CSCs stimulation and angiogenesis and effects were dose-dependent (Sordillo and Helson, 2015). Liposomal curcumin preparation exhibited anti-angiogenic effects in Colo205 xenografts by downregulating VEGF (Li *et al.,* 2007b). SF targeted pancreatic CSCs by inhibiting angiogenesis and downregulated VEGF and platelet-derived growth factor receptor-α (PDGFRα) expression. It also modulated Hh signaling pathway by inhibiting proteins involved in signal transduction

such as Gli-1, Gli-2 and SMO (Li *et al.*, 2013). EGCG downregulates VEGF expression and thus inhibits tumor growth and angiogenesis. It also modulates protein tyrosine kinase activity of EGFR and PDGFR, which act as a contributing factor in the proliferation of cancer (Larsen *et al.,* 2010). Experiments using EGCG in breast CSCs, colon cancer, pancreatic cancer cells and UV-induced skin tumors showed reduced VEGF expression and angiogenesis resulting in inhibition of tumor growth (Gu *et al.,* 2013; Kimura *et al.,* 2008; Mineva *et al.,* 2013; Shankar *et al.,* 2013).

Recent studies demonstrated inhibition of colon cancer-induced angiogenesis by capsaicin via suppression of STAT-3 mediated downstream targets. Capsaicin downregulated VEGF expression in NSCLC cells in a hypoxic environment through re-activated p53-SMAR1 positive feedback loop (Chakraborty *et al.*, 2014). *In vitro* and *in vivo* experiments on B16F-10 melanoma cells showed the antiangiogenic property of β-carotene by an alteration in cytokine profile and inhibition of activation and nuclear translocation of transcription factors (Guruvayoorappan and Kuttan, 2007). *In vitro* and *in vivo* studies using lycopene alone or with β-carotene supplementation suppressed the growth of lung cancer or prostate cancer cell line respectively by inhibiting angiogenesis (Palozza *et al.,* 2011; Yang *et al.,* 2011). Isoflavones inhibited Wnt signaling by enhancing the expression of glycogen synthase kinase-3 (GSK-3) followed by binding of GSK-3 to β-catenin leading to increased β-catenin phosphorylation and subsequently attenuated Wnt-induced proliferation (Amado *et al.,* 2011).

Reactive oxygen species (ROS) and anti-cancer effect

In recent years, researchers have shown that CSCs in various cancers contain lower level of ROS than their mature descendants and these differences are vital for maintaining stem cell

function (Diehn *et al.,* 2009). Based on the regulation of the ROS level in normal stem cells and CSCs, therapeutic application of ROS elevation to eliminate CSCs can be one of the important targets. Therefore, ROS act as "double-edged sword", by acting not only as disease inducers/sustainers but also as therapeutic weapons in cancer.

In spite of the contradictory roles of curcumin in scavenging and generating ROS, the overall effect of curcumin is an anticancer activity. Curcumin induced ROS production and BGC-823 cell apoptosis through oxidative stress-activated ASK1-MKK4-JNK signaling cascade (Park *et al.,* 2013b). Treatment of human renal Caki cells induced ROS and downregulated Bcl-xl and inhibitors of apoptosis proteins (IAP) (Woo *et al.,* 2003). In cervical cancer cell lines, curcumin generated ROS modified radiosensitivity via activated extracellular signal-regulated kinase (ERK) (Javvadi *et al.,* 2008). Curcumin treatment followed by purple light irradiation in human nasopharyngeal carcinoma (NPC) cells enhanced the cytotoxicity through potential induction of apoptosis and ROS generation (Wang *et al.,* 2013a). Curcumin and simvastatin may have anticancer and potential chemopreventive action through ROS-mediated apoptosis pathway in the lung cancer cell line. The mechanism of EGCG-induced apoptosis also involves upregulation of ROS. EGCG induced reactive oxygen species (ROS) and impaired the mitochondrial membrane potential (Satoh *et al*., 2013). Capsaicin-induced apoptosis in human colon cancer cell lines is associated with an increase in ROS generation and mitochondrial transmembrane potential disruption (Yang *et al*., 2009). Treatment of pancreatic cancer cell lines AsPC-1 and BxPC-3 with capsaicin resulted in a dose-dependent inhibition of cell-viability and induction of apoptosis which were associated with the generation of ROS and persistent disruption of mitochondrial membrane potential (Zhang *et al*., 2008). Piperlongumine (PPLGM),

a bioactive agent, found in long pepper repressed the growth of pancreatic cancer cell culture by elevating ROS level and caused DNA damage (Dhillon *et al*., 2014). A study in our lab demonstrated antioxidant activity of *Euphorbia hirta* extract and *in vitro* dose dependent anticancer activity against myeloid leukemia cell line (HL-60) (Sharma *et al*., 2014). Studies have revealed the dual role of lycopene as ROS scavenger and generator depending on its concentration. Lowe *et al.* (1999) found that oxidative DNA damage caused in HT29 cell line was protected by lower lycopene concentrations (1--3 μM) but increased by higher concentrations (4--10 μM).

Epigenetic alterations

Histone acetyltransferases (HATs), histone deacetylases (HDACs) and DNA methyltransferases (DNMTs) plays a central role in chromatin structure modification and thereby regulating transcription. While HAT activity is associated with transcriptionally active chromatin, DNMTs and HDACs causes gene silencing. An altered balance of DNA methylation and histone acetylation/deacetylation contributes to neoplastic transformation. Some of the most characterized signaling pathways such as Wnt/β-catenin, Hh, Notch and TGF-β/BMP pathways controlling self-renewal and differentiation in adult stem cells are frequently modulated in cancer by epigenetic mechanisms. Inhibitors of HDAC that have a broad spectrum of anticancer effects such as growth arrest, differentiation and apoptosis have attracted recent attention as potential anticancer agents.

Studies have suggested that the curcumin and EGCG anti-cancer activity is mediated partly through its epigenetic modulation by inhibition of DNMTs and HATs (Reuter *et al*., 2011). Phenyl isothiocyanate (PEITC) commonly found in cruciferous vegetables such as

mustard, radish, etc. has been described to stimulate apoptosis and cell cycle arrest in numerous cancer cells type. PEITC downregulated HDAC levels and activity and modified histone acetylation and methylation pattern (Thakur *et al*., 2014). PEITC caused demethylation of Glutathione S-transferase P (GSTP1) gene hypermethylated promoter region in prostate cancer cells. Lycopene caused partial demethylation of the promoter region of GSTP1 gene in MDA-MB-468 breast cancer cell lines (King-Batoon *et al*., 2008). Resveratrol suppressed CSCs properties of breast cancer cells by enhancing tumor suppressive miRNA functions through Argonaute 2 (Ago2) protein (Hagiwara *et al*., 2012). Resveratrol inhibited DNMT activity and reversed the methylation status of tumor suppressor genes in MCF7 breast cancer cells. It also improved the efficacy of adenosine analogs to inhibit RARβ2 gene promoter region methylation; however, resveratrol alone was ineffective (Stefanska *et al*., 2010). Resveratrol suppressed NPC CSCs by reactivation of the p53 pathway, miR-145, miR-200c induction and consequent inhibition of EMT (Shen *et al*., 2013).

Modulation of CSCs niche

CSCs reside within a specific niche and signaling between niche and the microenvironment govern its homeostasis and morphogenesis. It is the specialized niche microenvironment that helps in CSCs proliferation. Niche is characterized by hypoxia, low pH, oxidative stress and inflammation and is responsible for maintaining stem cell characteristics (Benito *et al.*, 2013; Hjelmeland *et al.*, 2011; Vera-Ramirez *et al.*, 2012). Targeting CSCs within the niche by changing microenvironment can be one of the important therapeutic strategies to cure cancer **(Fig. 4)**.

To counteract hypoxic environment within CSCs niche, hypoxia inducible factor (HIF-1) offers an attractive target that is found to be highly expressed within hypoxic tumor area (Pistollato *et al.,* 2010). Brucine (isolated from *Strychnos nux-vomica Linn.* seeds) repressed HepG2 and SMMC-7721 HCC cell migration significantly and attenuated HIF-1dependent target genes (fibronectin, matrix metallopeptidase 2, lysyl oxidase and cathepsin D) involved in metastasis (Shu *et al.,* 2013). Mulberry leaves extract downregulated HIF-1 gene and its downstream target gene expression in neuroblastoma cell line (Park *et al.,* 2013a). Few studies also demonstrated decreased survival of liver and breast cancer cell lines in a dose-dependent fashion by curcumin by inhibiting transcription of HIF-1α and HIF-1β genes (Bae *et al.,* 2006; Strofer *et al.,* 2011).

Persistent inflammation is the characteristic feature of CSC niche and is mediated by NF-κB signaling pathway and downstream targets, including cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), etc. Dietary phytochemicals such as flavonoids present in fruits and vegetables have demonstrated to inhibit NF-κB pathway and thus contribute to cancer prevention (Prasad *et al.,* 2010). Phytochemicals like SN, PEITC present in *Brassicaceae* suppressed COX-2 and prostaglandin E-2 (PGE2) in a mouse model of colon cancer (Kim *et al.,* 2009). Tea polyphenols such as EGCG induced anti-inflammatory effect in cancer cells by inhibiting NF-κB pathway and its downstream target genes COX-2 and iNOS (Upadhyay and Dixit, 2015).

CSCs microenvironment is characterized by low pH and promotes the expression of CSCs markers. Thus enhancing the niche pH can be one of the important therapeutic targets to inhibit malignant growth. Lu *et al*. (2014) demonstrated EGCG ability to target lactate

dehydrogenase-A (LDH-A) in human pancreatic adenocarcinoma MIA PaCa-2 cells. Observed results were comparable to Oxamate, a known inhibitor for LDH-A and exhibited anti-cancer activity by significantly modifying cancer metabolic phenotype. High-throughput screening of plant extracts demonstrated high activity of Kelp (*Laminaria japonica*), Chinese Gallnut (*Melaphis chinensis gallnut*) and Babul (*Acacia arabica*) in reducing lactate formation and release and emerged as the most effective LDH-A inhibitors (Deiab *et al.*, 2013). Shamim *et al.* (2012) demonstrated enhanced activity of Resveratrol at lower pH in Capan-2 and Panc-28 pancreatic cancer cell lines and observed enhanced DNA breakage. Preclinical studies using epigallocatechin isolated from *Spatholobus suberectus* in a mouse model of breast cancer demonstrated inhibition of LDH-A activity by disassociation of Hsp90 from HIF-1α and ensued accelerated HIF-1α proteasome degradation (Wang *et al.*, 2013c).

RESEARCH GAPS

Plentiful of *in vitro* and *in vivo* experiments have demonstrated curative and preventive potential of phytochemicals against cancer. Despite these facts, the biggest concern related to use of phytochemicals is the bioavailability of the active component at a therapeutic level to exert curative effects. The absorption of phytochemicals is generally lower and constituents are rapidly metabolized and excreted. It is relevant to characterize those factors modulating phytochemical absorption and bioavailbility. Development of novel analogs of these natural anticancer agents/ drug delivery system offers an alternative approach to enhance/improve bioavailabilty and thus can strengthen our efforts to fight against malignancy (Kasinski *et al.*, 2008). Another important aspect is the biostability of phytochemical constituents under physiological condition which limits its ability to reach target organs. Most of the *in vitro* and *in vivo* studies are conducted at

supra-physiological concentration. In line with the basic principle of toxicology, high dose of any compound is toxic and phytochemicals based treatment are no exception and long term studies are warranted to delineate the safety profile of phytochemicals under investigation (Galati *et al.,* 2006; Lambert *et al.,* 2007). Therefore, it would be pertinent to identify physiologically attainable concentrations of dietary phytochemicals in human subjects and epidemiological studies along with clinical trials would be highly beneficial to demonstrate anti-tumor effects of plant derived compounds.

CONCLUSIONS

The emergence and validity of CSCs have made a paradigm shift in cancer research with a revisit of therapeutic strategies to cure malignancies. Stemness properties of self-renewal and differentiation warrant compounds that can inhibit CSCs above capacities without affecting normal stem cells and is the need of the hour to strengthen our fight against malignancy. Unwarranted side effects with synthetic anticancer drugs have driven researchers to look towards nature and explore their potential in eliminating cancer, particularly CSCs. Numerous *in vitro* and *in vivo*, preclinical cancer prevention and treatment studies have been performed to evaluate the potential of phytochemicals with varying success rates. Phytochemicals being a cocktail of many active ingredients, target multiple pathways distressing different cell signaling processes altered in malignant cells and may help to kill cancer cells with lesser chances of developing drug resistance. Some of the few studies demonstrated the synergistic effect of phytochemicals with chemotherapy or radiotherapy resulting in reduced doses and toxicity. It is probable that some of these phytochemicals, their analogs and development of improved drug delivery systems may finally provide the solution for eliminating CSCs and will strengthen our armor to fight

against cancer. Natural dietary phytochemicals continue to be promising and active research area in the future and with demonstrable anti-tumorigenesis effects and targets on self-renewal pathways of CSCs; offers new avenues for cancer prevention and treatment.

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COMPETING INTERESTS

The authors declare no competing interests.

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Table 1: Cancer and expressed stem cell markers distribution

Cancer	Cell surface markers	Reference
Brain	CD133, ABCG 2	(Cheng *et al.,* 2009), (Islam *et al.,* 2005)
Breast	ALDH1, CD44	(Croker *et al.,* 2009), (Al-Hajj *et al.,* 2003)
Colorectal	CD133, CD44, ALDH1	(Jaksch *et al.,* 2008), (Dalerba *et al.,* 2007), (Schwartz *et al.,* 2013)
Gastric	ALDH1	(Zhi *et al.,* 2011)
Glioma	CD90	(He *et al.,* 2012)
Leukemia	CD34, CD19	(Bapat *et al.,* 2005)

Liver	CD133, CD90, ALDH1, BCG2	(Ding *et al.,* 2009), (Shi *et al.,* 2008a), (Ma *et al.,* 2008), (Yang *et al.,* 2008)
Lung	CD133, ALDH1, CD44, CD24	(Bertolini *et al.,* 2009), (Jiang *et al.,* 2009), (Jaggupilli and Elkord, 2012)
Melanoma	CD133, ABCB5, CD20	(Jaksch *et al.,* 2008), (Gazzaniga *et al.,* 2010), (Schmidt and Abken, 2011)

Ovary	CD133, ABCG2	(Stewart *et al.,* 2011), (Dou *et al.,* 2011)
Pancreas	CD133, ALDH1, CD44, BCG2	(Immervoll *et al.,* 2008), (Tomuleasa *et al.,* 2011), (Li *et al.,* 2007a), (Apati *et al.,* 2008)

Table 2: Dietary phytochemicals and their molecular targets

Phytochemicals	Molecular targets
Curcumin	ABCG2, ABCB1, ABCC1, Wnt/ β-Catenin, P-gp, MRP1, Akt/mTOR, apoptosis, Hedgehog, NF-κB, Notch, p53, VEGF, DNMTs, HATs
Epigallocatechin gallate (EGCG)	P-gp, Wnt, apoptosis, cell cycle, Hedgehog, Akt/mTOR, NF-κB, VEGF
Sulforaphane	NF-κB, Akt/mTOR, ALDH1, Wnt, apoptosis, EMT
Resveratrol	Apoptosis, Wnt, Akt/mTOR, NF-κB, Notch, p53, DNMTs
Lycopene	Akt/mTOR, VEGF, epigenetic alterations
Quercetin	Apoptosis, Wnt, Hedgehog, NF-κB, PI3K/Akt, MRP1, 4, and 5

ALDH1, *Aldehyde dehydrogenase 1*; **ABCB1**, *ATP-binding cassette, sub-family B (MDR/TAP), member 1*; **ABCC1**, *ATP-binding cassette, sub-family C (MDR/TAP) member 1;* **ABCG2**, *ATP-binding cassette transporter G2;* **DNMTs**, *DNA methyltransferases*; **EMT**, *Epithelial-mesenchymal transition****;*** **HATs,** *Histone acetyltransferases*; ***MRP,*** *Multidrug resistance-related protein;* **mTOR**, *Mammalian target of rapamycin****; NF-κB****, Nuclear factor-kappa B;* ***P-gp****, P-glycoprotein;* **VEGF**, *Vascular endothelial growth factor*

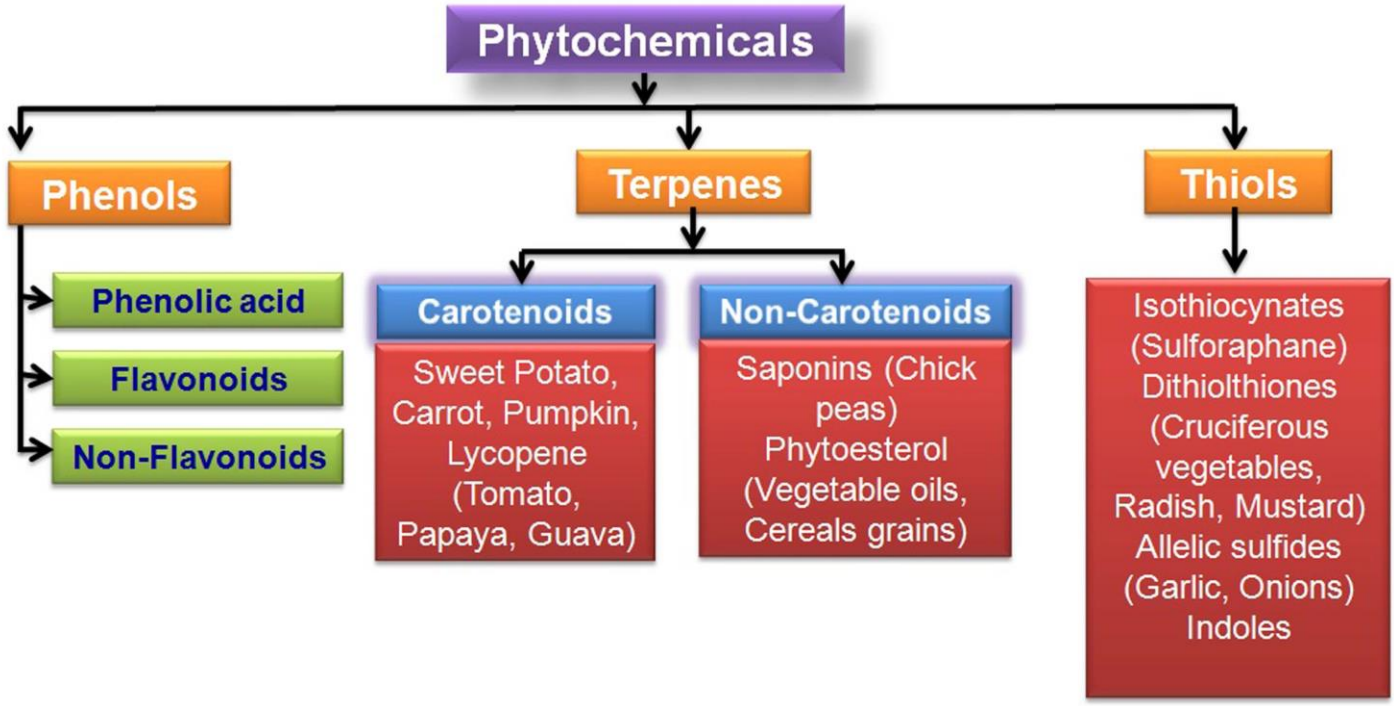


Figure 1: Classification of dietary phytochemicals

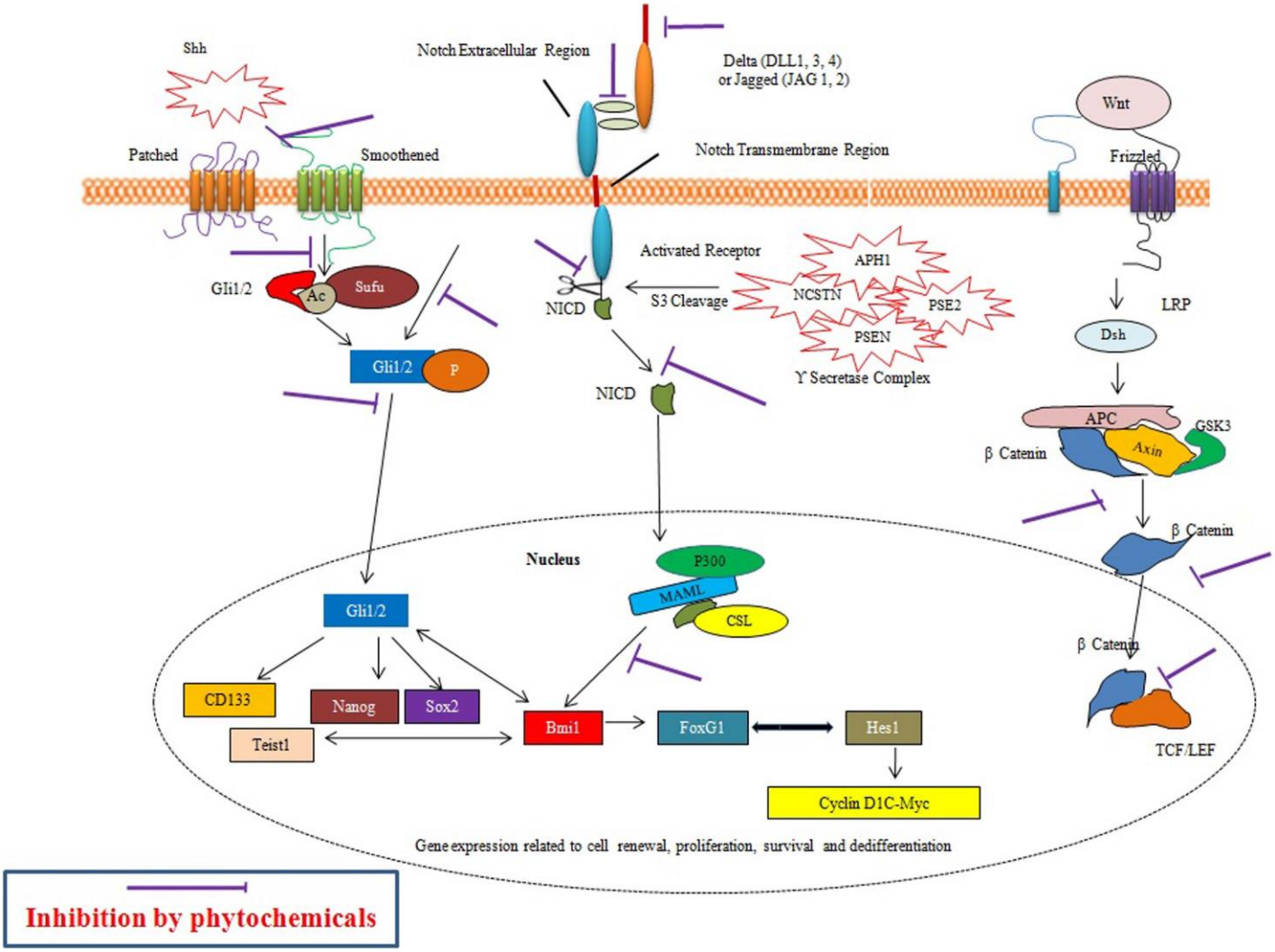


Figure 2: Effect of phytochemicals on cancer stem cells. During signaling process, Delta ligand binds with Notch receptor and lead to cleavage of cytoplasmic tail by γ-secretase complex. The cytoplasmic tail called Notch Intracellular Domain (NICD) translocates to the nucleus, a process that is known to be inhibited by multiple phytochemicals. Binding of Hh ligand to PTCH receptor leads to SMO localization to the plasma membrane and prevents degradation of Gli. Gli translocates to the nucleus and activates transcription of Hh responsive genes, a pathway interrupted by numerous phytochemicals. Wnt Interaction with its receptor

Frizzled activates Dishevelled (DSH) and lead to the inhibition of APC/Axin/GSK3 β -mediated β-catenin degradation by E3 ubiquitin ligase. Phytochemicals block β--catenin mediated signaling by blocking Wnt/Dvl-mediated inactivation of GSK3 β, inhibiting nuclear translocation of β -catenin, and/or blocking the formation of β -catenin-TCF/LEF complex and transcriptional activation of target genes.

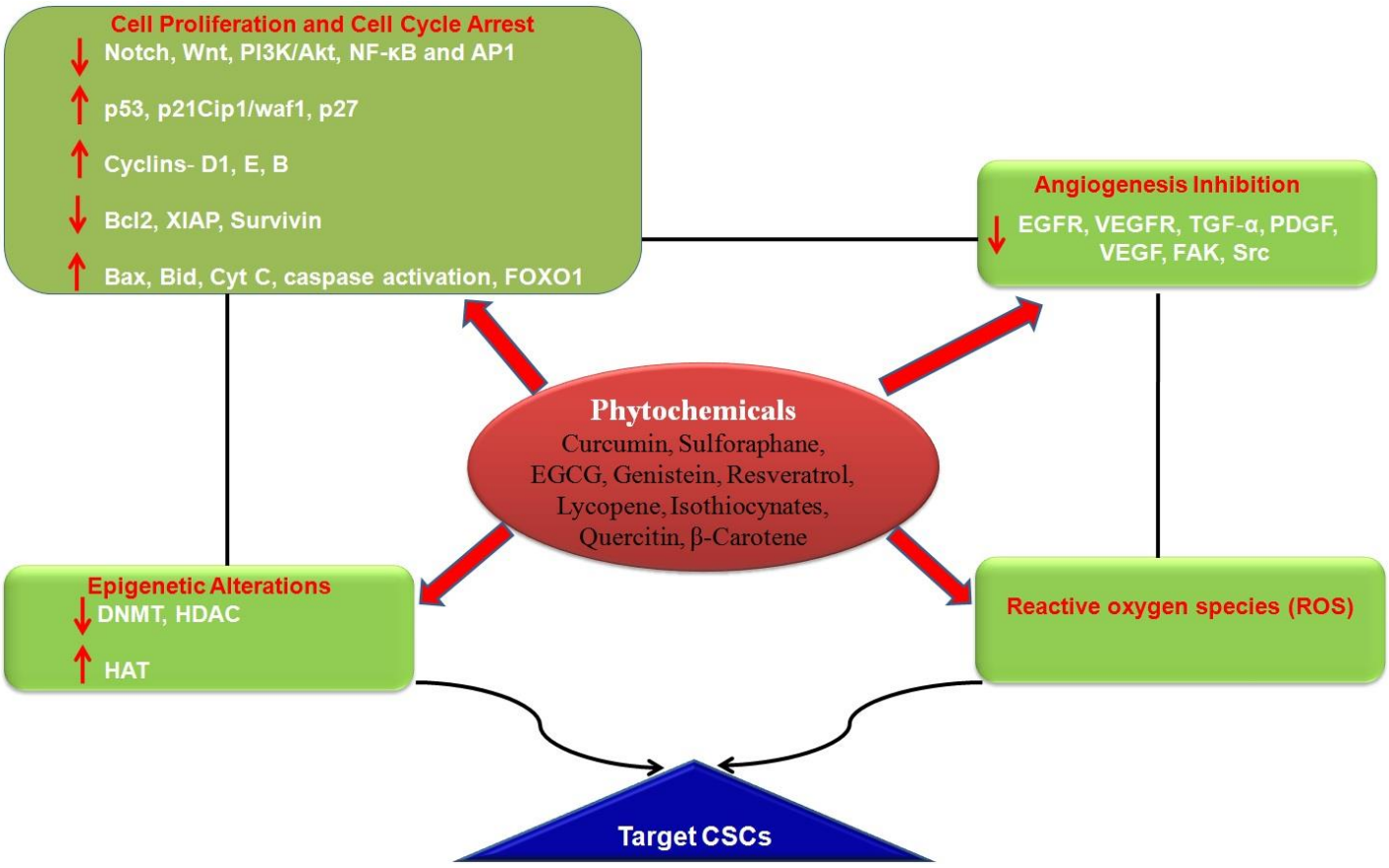
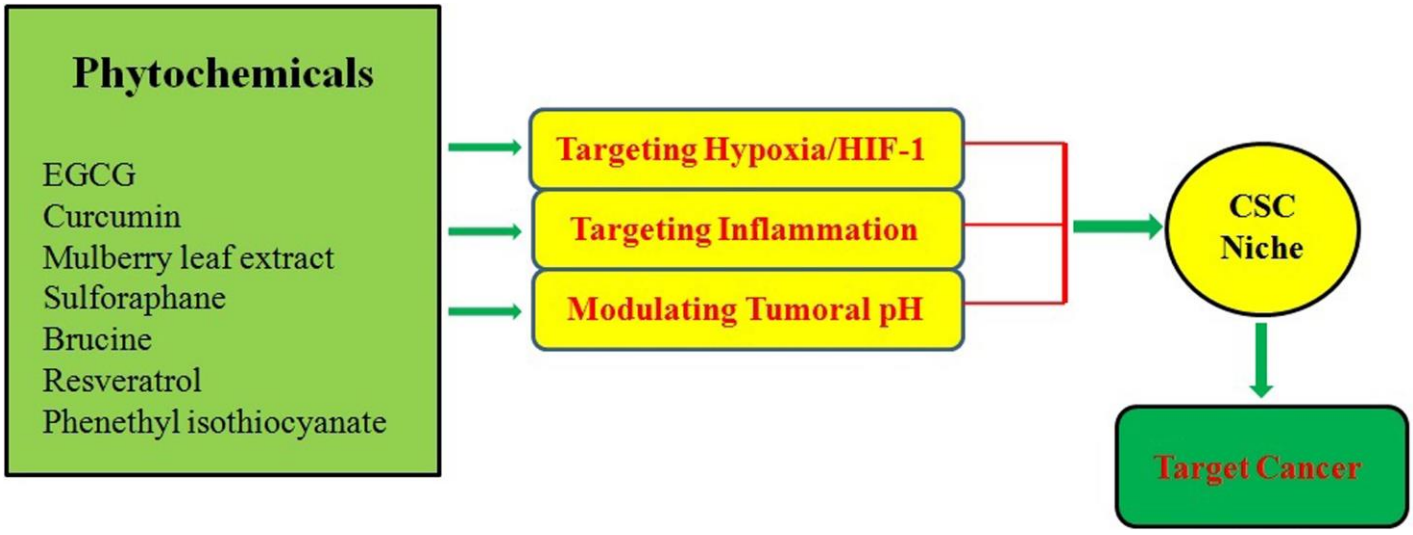


Figure 3: The antitumor effect of dietary phytochemicals via multiple molecular targets. Plant derived compounds influenced CSCs stemness property and self-renewal capacity. Several phytochemicals have the ability to downregulate cell proliferation and cell cycle progression by modulating self-renewal pathways (e.g. Notch, Wnt, cyclins, etc.) or promoting apoptosis through enhancement of apoptotic proteins (Bax, Bid, Caspase, etc) or via downregulation of anti-apoptotic proteins (Bcl2, XIAP, etc). Phytochemicals inhibit angiogenesis via downregulation of gene expression (EGFR, VEGF, etc.), regulate epigenetic alterations through upregulation (HAT) or downregulation (DNMT, HDAC). They also promote reactive oxygen

species (ROS) production and thereby eradicate CSCs/prevent cancers. **Abbreviations:** Bax, Bcl-2-associated X protein; Bid, BH3 interacting-domain death agonist; Bcl-2, B-cell lymphoma 2; XIAP, X-linked inhibitor of apoptosis protein; EGFR, Epidermal growth factor receptor; VEGF, Vascular endothelial growth factor; DNMT, DNA methyltransferase; HDAC, Histone deacetylase; HATs, Histone acetyltransferases.



Figures 4: Dietary Phytochemicals modulates cancer stem cell niche CSCs niche has low pH, the presence of hypoxic and inflammatory conditions. Phytochemicals target these pathways by reducing HIF-1 gene and its downstream target gene expression, NF-κB pathway to modulate inflammatory reactions and hinder LDH-A gene expression to increase tumoral pH.