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# Potential Application of Natural Dietary Components to Target Cancer Stem Cells

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## 1. Introduction

The emergence of cancer stem cell (CSC) theory has profound implications for cancer prevention and therapy. Although a large majority of chemotherapeutic drugs can considerably shrink tumor sizes (Reya et al. 2001), they often fail to eradicate tumors due to the inability to effectively kill CSCs (Reya et al. 2001; Hambardzumyan et al. 2006; Shafee et al. 2008; Korkaya et al. 2009). The cancer may eventually develop drug resistance and recurrence (Williams et al. 1987; Lippman 2000; Stockler et al. 2000; Reya et al. 2001; Zhou, B. B. et al. 2009). Therefore, the CSC population has become a promising target for cancer prevention and therapy (Zhou, B. B. et al. 2009).

Since a large number of epidemiological studies have demonstrated an association between consumption of fruits and vegetables and the reduced risk of various cancers, naturally-occurring dietary components have received considerable attention for their effects in cancer chemoprevention (Smith-Warner et al. 2003). The anti-cancer activities of many dietary components against various types of cancer have been reported for both *in vitro* and *in vivo* studies (Chinni et al. 2001; Mukhopadhyay et al. 2001; Choudhuri et al. 2002; Lamartiniere et al. 2002; Li and Sarkar 2002; Gupta, S. et al. 2003; Hastak et al. 2003; Li et al. 2003). Recently, a number of studies have found that several dietary components can directly or indirectly affect CSC self-renewal pathways (Kawasaki et al. 2008), and thus may have potential impact on CSCs. This chapter reviews current attempts to target CSCs with bioactive dietary components, with a special emphasis on our work.

## 2. Self-renewal pathways of CSCs

CSCs produce the tumor mass through continuous self-renewal and differentiation, which may be regulated by similar signaling pathways occurring in normal stem cells (Reya et al. 2001; Liu, S. et al. 2005). Understanding the mechanisms that underlie the self-renewal behavior of CSCs is of greatest importance for discovery and development of agents targeting CSCs. So far, several major pathways including Wnt/β-catenin, Hedgehog, and Notch have been identified to play pivotal roles in CSC self-renewal (Smalley and Dale 1999; Dontu et al. 2004; Liu, S. et al. 2006).

### 2.1 Wnt/β-catenin pathway

Wnt/β-catenin pathway was demonstrated to modulate cell proliferation, migration, apoptosis, differentiation, and CSC self-renewal (Akiyama 2000; Polakis 2000; Yamaguchi 2001; Turashvili et al. 2006). It has been shown that Wnt/β-catenin signaling is implicated in the maintenance of CSCs of leukemia (Ysebaert et al. 2006; Khan et al. 2007; Kawaguchi-Ihara et al. 2008), melanoma (Chien et al. 2009), breast (Li et al. 2003; Woodward et al. 2007), colon (Schulenburg et al. 2007), liver (Yang, W. et al. 2008), lung (Teng et al. 2010) cancers. For example, over-expression of β-catenin in stem cell survival pathway was shown to mediate the resistance of mouse mammary stem/progenitor cells to radiation (Woodward et al. 2007). Yang and his colleagues reported that Wnt/β-catenin signaling promoted expansion of the hepatic progenitor cell population when it is over-expressed in transplanted rat oval cells and when it is transiently expressed in adult mice (Yang, W. et al. 2008). Elimination of β-catenin abrogated the chemo-resistant cell population endowed with progenitor-like features (Yang, W. et al. 2008).

β-Catenin, the essential mediator of canonical Wnt signaling, participates in two distinct functions in the cell, depending on its cellular localization. Membrane-localized β-catenin is sequestered by the epithelial cell-cell adhesion protein E-cadherin to maintain cell-cell adhesion (Nelson and Nusse 2004). On the other hand, cytoplasmic accumulation of β-catenin and its subsequent nuclear translocation, followed by cooperation with the transcription factors T cell factor/lymphoid enhancer factor (TCF/LEF) as a transcription activator, eventually leads to activation of Wnt target genes such as *c-Jun*, *c-Myc*, *fibronectin*, and *cyclin D1* (He et al. 1998; Mann et al. 1999; Orsulic et al. 1999; Tetsu and McCormick 1999; Lin, S. Y. et al. 2000; Liu, S. et al. 2005; Clevers 2006). Binding of Wnt proteins, a family of secreted proteins, to Frizzled receptors results in the cytoplasmic accumulation of β-catenin (Schweizer and Varmus 2003). In the absence of Wnt signaling, β-catenin forms a multi-protein complex with glycogen synthase kinase 3β (GSK3β), adenomatous polyposis coli, casein kinase1α, and axin (Takahashi-Yanaga and Sasaguri 2008). When β-catenin is phosphorylated at Ser33/Ser37/Thr41 by GSK3β, it is immediately subject to ubiquitin-proteasome degradation (Liu, C. et al. 2002; Takahashi-Yanaga and Sasaguri 2008).

The link between Wnt/β-catenin and PI3K/Akt pathway has been established by several studies. Activated Akt (i.e., phospho-Akt Ser473) was shown to be able to phosphorylate Ser9 on GSK3β, which may decrease the activity of GSK3β, thereby stabilizing β-catenin (Yost et al. 1996; Pap and Cooper 1998; Cohen, P. and Frame 2001). Furthermore, Korkaya et al. demonstrated that PI3K/Akt pathway is important in regulating the mammary stem/progenitor cells by promoting β-catenin downstream events through phosphorylation of GSK3β (Korkaya et al. 2009).

### 2.2 Hedgehog pathway

Another critical pathway that is involved in CSC self-renewal is hedgehog signaling pathway (Cohen, M. M., Jr. 2003; Liu, S. et al. 2006; Clement et al. 2007; Charafe-Jauffret et al. 2008). For instance, Liu et al. have demonstrated that the hedgehog pathway plays a crucial role in regulating self-renewal of normal and malignant human mammary stem cells by utilizing both *in vitro* and mouse model systems (Liu, S. et al. 2006). Another recent study revealed the essential role of hedgehog-Gli signaling in controlling the self-renewal behavior of human glioma CSCs and tumorigenicity (Clement et al. 2007).

In the absence of hedgehog ligands (Sonic Hedgehog, Desert Hedgehog, and Indian Hedgehog), their transmembrane receptor Patched (Ptch) associates with Smoothened (Smo) and blocks Smo function (Cohen, M. M., Jr. 2003; Lewis and Veltmaat 2004; Liu, S. et al. 2005). When secreted hedgehog ligands bind to Ptch, Smo is released, triggering dissociation of transcription factors, Gli1, Gli2, and Gli3 from Fused (Fu) and suppressor of Fused (SuFu), leading to transcription of an array of genes, such as *cyclin D*, *cyclin E*, *Myc*, and elements of EGF pathway (Cohen, M. M., Jr. 2003; Pasca di Magliano and Hebrok 2003; Lewis and Veltmaat 2004; Liu, S. et al. 2005).

Sonic hedgehog pathway is also linked to transcription factor NF-κB signaling. NF-κB was suggested to be a prominent factor in controlling tumor growth and apoptosis resistance of pancreatic CSCs (Kallifatidis et al. 2009). Over-expression of sonic hedgehog is activated by NF-κB in pancreatic cancer and pancreatic cancer cell proliferation is accelerated by NF-κB in part through sonic hedgehog over-expression (Nakashima et al. 2006). Kasperczyk et al. further characterized sonic hedgehog as a novel NF-κB target gene and mapped minimal NF-κB consensus site to position +139 of sonic hedgehog promoter (Kasperczyk et al. 2009).

### 2.3 Notch pathway

Notch signaling is known to control cell proliferation and apoptosis to modulate the development of many organs (Wang, Z. et al. 2009). A number of recent studies have demonstrated that Notch-activated genes and pathways can drive tumor growth through the expansion of CSCs (Wilson and Radtke 2006; Charafe-Jauffret et al. 2008; Fan and Eberhart 2008; Kakarala and Wicha 2008; Peacock and Watkins 2008; Scoville et al. 2008; Wang, Z. et al. 2009). Notch pathway is believed to be dysregulated in CSCs, ultimately leading to uncontrolled CSC self-renewal (Wang, Z. et al. 2009). For example, Notch pathway was shown to play an important role in the self-renewal function of malignant breast cancer CSCs (Dontu et al. 2004; Farnie and Clarke 2007).

Five Notch proteins, Notch-1 to Notch-4, have been identified to express as transmembrane receptors in a variety of stem/progenitor cells (Mumm and Kopan 2000). Binding of surface-bound ligands (Jagged1, Jagged2, Delta-like1, Delta-like3, and Delta-like4) triggers serial cleavage events at the Notch proteins by ADAM protease family and γ-secretase (Wu, J. Y. and Rao 1999; Mumm and Kopan 2000; Borggrefe and Oswald 2009). Subsequently, the intracellular domain of Notch is released and translocates into the nucleus, where it acts as a transcription co-activator of recombination signal sequence-binding protein Jκ (RBP-J) to activate downstream target genes, e.g., *c-Myc*, *cyclin D1*, *p21*, *NF-κB* (Oswald et al. 1998; Rangarajan et al. 2001; Ronchini and Capobianco 2001; Satoh et al. 2004; Palomero et al. 2006; Weng et al. 2006; Borggrefe and Oswald 2009).

Notch1 has been reported to be the upstream regulator of NF-κB pathway in diverse cellular situations (Oswald et al. 1998; Wang, J. et al. 2001; Nickoloff et al. 2002; Dontu et al. 2004; Jang et al. 2004; Wang, Y. et al. 2004; Shin et al. 2006; Wang, Z. et al. 2006; Chen et al. 2007). Specifically, Notch-1 is necessary for expression of several NF-κB subunits (Cheng et al. 2001; Jang et al. 2004) and stimulates NF-κB promoter activity (Jang et al. 2004).

## 3. Sulforaphane

Numerous studies have substantiated the chemopreventive properties of high consumption of cruciferous vegetables, especially broccoli and broccoli sprouts, against various types of

cancer (Clarke et al. 2008). Cruciferous vegetables are characterized by their high content of glucosinolates (Herr and Buchler 2010; Fahey et al. 2001), which are converted to isothiocyanates by the action of myrosinase. The chemopreventive effects have been mostly attributed to the activity of these isothiocyanates (Zhang et al. 1992; Clarke et al. 2008). In particular, sulforaphane (Figure 1) is converted from glucoraphanin, the principal glucosinolate in broccoli and broccoli sprouts (Fahey et al. 1997). Sulforaphane has been shown to be not only effective in preventing chemically induced cancers in animal models, including colon, lung, breast, pancreatic, skin and stomach cancer (Zhang et al. 1994; Fahey et al. 1997; Chung et al. 2000; Fahey et al. 2002; Conaway et al. 2005; Gills et al. 2006; Kuroiwa et al. 2006; Xu et al. 2006), but also inhibit the growth of established tumors (Jackson and Singletary 2004; Singh, A. V. et al. 2004).

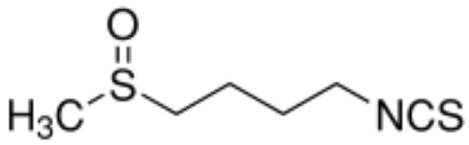


Fig. 1. Chemical structure of sulforaphane

Early research focused on inhibition of Phase 1 metabolism enzymes that convert procarcinogens to carcinogens and induction of Phase 2 metabolism enzymes that enhance elimination and excretion of carcinogens by sulforaphane (Clarke et al. 2008), which enhances the detoxification of carcinogens and "blocks" carcinogenesis at the initiation stage of cancer (Juge et al. 2007; Clarke et al. 2008).

Subsequent studies suggest that sulforaphane provides protection against tumor development during the "post-initiation" phase by modulating diverse cellular activities including apoptosis, cell cycle, angiogenesis and metastasis (Zhang and Tang 2007; Clarke et al. 2008). Sulforaphane affects classical molecular targets involved in the apoptosis pathways such as down-regulation of anti-apoptotic Bcl-2 and Bcl-$_{XL}$, up-regulation of pro-apoptotic Bax expression, proteolytic activation of caspase-3, and the degradation/cleavage of poly(ADP-ribose) polymerase, induction of apoptotic protease activating factor-1 (Choi et al. 2007; Park, S. Y. et al. 2007). The ability of sulforaphane to induce cell cycle arrest is associated with regulation of many molecules including cyclins, Cdks, and p21 (Singh, S. V. et al. 2004; Herman-Antosiewicz et al. 2007; Zhang and Tang 2007). More recent studies demonstrate that sulforaphane is also capable of suppressing angiogenesis and metastasis, which are associated with transcriptional down-regulation of vascular endothelial growth factor (VEGF), hypoxia-inducible factor-1α (HIF-1α), c-Myc and matrix metalloproteinase-2 (MMP-2), and MMP-9 (Bertl et al. 2006; Zhang and Tang 2007).

Our studies have shown that sulforaphane is effective in targeting breast CSCs *in vitro* and *in vivo* (Li et al. 2010). Mammosphere culture was first used to isolate and expand mammary stem/progenitor cells by Dontu et al., based on the ability of stem/progenitor cells to grow in serum-free, non-adherent suspension as spherical clusters of cells while differentiated cells fail to survive under the same condition (Dontu et al. 2003). By employing this technique, we demonstrated that sulforaphane (0.5-5 μM) significantly suppressed the mammosphere formation of both SUM159 and MCF7 cells. A decrease in the number of sphere-forming cells in the 2nd and 3rd passages indicated a reduced self-renewal capacity of these stem/progenitor cells (Dontu et al. 2003). In breast carcinomas, a cell population

with high aldehyde dehydrogenase (ALDH) activity as assessed by the Aldefluor assay has been demonstrated to enrich tumorigenic stem/progenitor cells (Ginestier et al. 2007). This cell population is capable of self-renewal and generating tumors resembling the parental tumor (Ginestier et al. 2007). We found that sulforaphane (1-5 μM) was able to significantly decrease the tumor-initiating ALDH-positive cell population of SUM159 by 65% to 80% *in vitro*. Of special note, concentrations of sulforaphane which inhibit stem/progenitor cells in both mammosphere formation assay and Aldefluor assay had only minimal effects on the bulk population of breast cancer cell lines, implying that sulforaphane is likely to preferentially target stem/progenitor cells compared to the differentiated cancer cells.

We further demonstrated that sulforaphane can inhibit breast CSCs *in vivo* (Li et al. 2010). The injection of human breast cancer cells into the mammary fat pad of immune-deficient NOD/SCID mice provides a reliable and sensitive *in vivo* system for studying human breast cancer (Al-Hajj et al. 2003; Dick 2003). Daily injection of sulforaphane for two weeks suppressed tumor growth in primary NOD/SCID mice and reduced ALDH-positive cell population of the tumors by more than 50%. Most importantly, we found that recipient NOD/SCID mice inoculated with tumor cells derived from sulforaphane-treated primary xenografts largely failed to develop tumor re-growth up to 33 days, whereas control tumor cells quickly initiated new tumors upon re-implantation. These results suggest that sulforaphane is able to eliminate breast CSCs *in vivo*, thereby abrogating tumor re-growth after re-implantation of primary tumor cells into the secondary mice.

We also observed a down-regulation of Wnt/β-catenin self-renewal pathway in sulforaphane-treated breast cancer cells (Li et al. 2010). Park et al. previously reported that β-catenin was down-regulated by sulforaphane in human cervical carcinoma HeLa and hepatocarcinoma HepG2 cells (Park, S. Y. et al. 2007). In consistent with their study, we showed that sulforaphane was able to down-regulate Wnt/β-catenin self-renewal pathway in breast cancer cells, and sulforaphane-induced β-catenin phosphorylation (Ser33/Ser37/Thr41) and proteasome degradation was possibly through activation of GSK3β. The down-regulation of Wnt/β-catenin self-renewal pathway might contribute to the inhibitory effects of sulforaphane on breast CSCs. Further studies are warranted to establish the conclusive role of this down-regulation in inhibition of breast CSCs by sulforaphane.

In addition, our recent work has revealed a new molecular target of sulforaphane. Sulforaphane inhibits heat shock protein 90 (Hsp90) function by blocking the interaction of Hsp90 with it cochaperone $p50^{Cdc37}$, and we traced this activity to a novel interaction site of Hsp90, which fundamentally differs from the mechanism of other Hsp90 inhibitors (unpublished data). LC-MS peptide mapping identified a covalent adduct of sulforaphane with a short peptide IDIIPNPQER in Hsp90 N-terminal domain. NMR experiment with full-length Hsp90 revealed sulforaphane interaction in sheet 2 and the adjacent loop in Hsp90 N-terminal domain, in which this short peptide resides. Akt is a well-known Hsp90 client protein. Our and several other studies have reported the activity of sulforaphane to down-regulate the protein level of Akt and Akt pathway in ovarian, prostate, and colorectal cancers (Chaudhuri et al. 2007; Shen et al. 2007; Shankar et al. 2008). PI3K/Akt pathway was recently demonstrated to play an important role in regulating breast stem/progenitor cells by promoting β-catenin down-stream events through phosphorylation of GSK3β (Korkaya et al. 2009). Therefore, inhibition of Hsp90 chaperone function by sulforaphane may contribute to the effect on Akt/GSK3β/β-catenin pathway.

The resistance of pancreatic cancer toward TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) is due to TRAIL-activated NF-κB signaling (Ibrahim et al. 2001). Kallifatidis et al. demonstrated that sulforaphane (10 μM) was able to deplete pancreatic CSCs ($CD44^+CD24^-$) by interfering with NF-κB binding and abrogating apoptosis resistance (Kallifatidis et al. 2009). They found that the presence of pancreatic TICs correlated with apoptosis resistance towards TRAIL due to the enhanced binding of NF-κB complexes to DNA. Sulforaphane alone or in combined with TRAIL reduced growth of $TIC^{high}$ tumors *in vivo* without toxicity to normal tissue.

Like TRAIL, sorafenib was also observed to strongly up-regulate NF-κB activity (Rausch et al. 2010). Sulforaphane (10 μM) completely abolished sorafenib-induced NF-κB binding in $CSC^{high}$ cells, thereby synergistically inhibiting pancreatic CSC ($CD44^+CD24^-$) (Rausch et al. 2010). The growth of pancreatic $CSC^{high}$ tumor xenografts was synergistically inhibited by combination of sulforaphane and sorafenib, which involved induction of apoptosis, inhibition of proliferation and angiogenesis, as well as down-regulation of epithelial-mesenchymal transition (EMT) related proteins (vimentin, Zeb-1, and Twist-2). EMT induction in cancer cells results in the acquisition of invasive and metastatic properties (Singh, A. and Settleman 2010; Gupta, P. B. et al. 2009; Klarmann et al. 2009; Sarkar et al. 2009). CSCs undergoing metastasis usually express EMT markers (Tang et al. 2010).

This same group then combined sulforaphane (5 μM) with several chemotherapeutic drugs and observed increased cytotoxicity toward pancreatic CSCs ($CD44^+CD24^-$) (Kallifatidis et al. 2011). Sulforaphane not only down-regulated basal Notch-1 expression in $CSC^{high}$ cells, but also prevented the gemcitabine-induced Notch-1 up-regulation. There was no tumor growth in mice re-implanted with tumor cells derived from sulforaphane-treated or combination-treated xenografts.

Another recent study also examined the molecular mechanisms by which sulforaphane inhibits growth and induces apoptosis of pancreatic CSCs (Srivastava et al. 2011). They demonstrated that sulforaphane (5-10 μM) inhibited self-renewal capacity of pancreatic CSCs ($CD44^+CD24^+ESA^+$). Sulforaphane induced apoptosis by inhibiting the expression of Bcl-2 and XIAP, phosphorylation of FKHR, and activating caspase-3. Moreover, sulforaphane inhibited expression of EMT markers (β-catenin, vimentin, Twist-1, and Zeb-1), suggesting the blockade of early metastasis signaling.

In summary, all of these findings strongly support that combination of sulforaphane or even broccoli/broccoli sprout preparations with chemotherapy may be a promising strategy to eradicate tumors and improve patient survival in different types of cancer.

## 4. Curcumin

Curcumin (Figure 2) is a dietary polyphenol present in the Indian spice turmeric, which is produced from rhizome of the plant *Curcuma longa* and usually used in preparation of mustard and curry (Park, C. H. et al. 2005). Curcumin has been studied as a chemoprevention agent in several cancer models (Mukhopadhyay et al. 2001; Shao et al. 2002; Lin, J. K. 2007; Anand et al. 2008; Kunnumakkara et al. 2008; Strimpakos and Sharma 2008).

Curcumin has been shown to regulate many cellular pathways (Lin, J. K. 2007; Hatcher et al. 2008; Kunnumakkara et al. 2008; Sa and Das 2008; Ravindran et al. 2009), some of which are associated with self-renewal signaling. Curcumin was suggested to induce caspase-3-mediated cleavage of β-catenin, leading to inactivation of Wnt/β-catenin signaling in

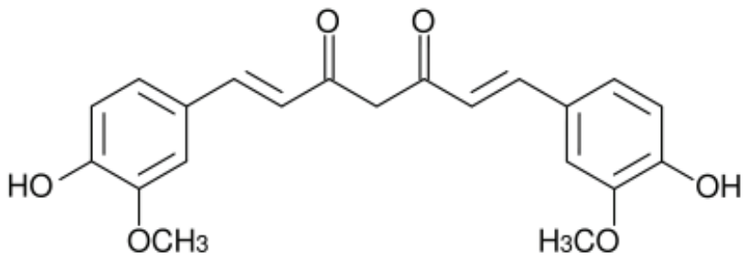


Fig. 2. Chemical structure of curcumin

HCT116 intestinal cancer cells (Jaiswal et al. 2002). The work of Park et al. strengthened the point that curcumin decreased β-catenin/TCF transcription activity in all tested cancer cell lines, including gastric, colon, and intestinal cancer cells, which was attributed to the reduced amount of nuclear β-catenin and TCF-4 proteins (Park, C. H. et al. 2005). Moreover, analysis of gene transcription profile revealed that the expression of Wnt receptor Frizzled-1 was potently suppressed by curcumin (Yan et al. 2005). Curcumin was also shown to be able to attenuate response of β-catenin to Wnt-3a in colon cancer cells through down-regulation of p300, a positive regulator of Wnt/β-catenin signaling (Ryu et al. 2008). In addition, Wang and his colleagues demonstrated that curcumin down-regulated Notch-1 mRNA level in pancreatic cancer cells, indicating a transcriptional inactivation of Notch-1 by curcumin (Wang, Z. et al. 2006). AP-1 and NF-κB signaling pathways were shown to be inhibited by curcumin in glioblastoma cells (Dhandapani et al. 2007). Curcumin-induced inactivation of NF-κB DNA-binding activity was potentially mediated by Notch-1 signaling pathway (Wang, Z. et al. 2006).

Kakarala et al. demonstrated that curcumin (5-10 μM) was able to target breast stem/progenitor cells, as evidenced by suppressed mammosphere formation along serial passage and a decrease in the percentage of ALDH1-positive cells (Kakarala et al. 2009). Similar to sulforaphane, the concentrations of curcumin inhibiting mammosphere formation was much lower compared to the concentrations of curcumin having impact on differentiated cells. Results from serial passaging suggest that curcumin interferes with breast CSC self-renewal. By utilizing a TCF-LEF reporter assay system in MCF7 cells, the authors confirmed that the effect of curcumin on breast cancer stem/progenitor cells was mediated through its potent inhibitory effect on Wnt/β-catenin signaling (Kakarala et al. 2009). These results support the work in other systems showing the ability of curcumin to inhibit Wnt signaling (Jaiswal et al. 2002; Ryu et al. 2008; Prasad et al. 2009). The effects of curcumin was further potentiated by piperine, another dietary polyphenol isolated from back and long peppers (Kakarala et al. 2009). Piperine was suggested to enhance the bioavailability of curcumin through inhibition of P glycoprotein-mediated efflux of curcumin (Shoba et al. 1998; Chearwae et al. 2004; Anand et al. 2007; Limtrakul et al. 2007). Curcumin and piperine, alone or in combination did not cause toxicity to differentiated cells (Kakarala et al. 2009).

Side population (SP) cells, first identified for isolation of murine hematopoietic stem cells from bone marrow (Goodell et al. 1996; Zhou, S. et al. 2001; Hirschmann-Jax et al. 2004), can be used to enrich CSCs (Hadnagy et al. 2006; Wu, C. and Alman 2008). Curcumin inhibited SP of the rat C6 glioma at low concentration (5 μM) that had minimal effect on proliferation of C6 cells (Fong et al. 2010). Very recently, a polymeric nanoparticle formulation of curcumin (5-20 μM) was shown to significantly inhibit clonogenicity and depleted the $CD133^+$ stem-

like cell population from brain tumor cultures (Lim et al. 2011). They also found that Gli1 and Ptch1B, two key components of hedgehog signaling, were significantly reduced in embryonal tumor derived cell line DAOY after curcumin treatment.

## 5. Epigallocatechin-3-gallate (EGCG)

Green tea is one of the most widely consumed beverages in the world. Epidemiological studies suggest an association between green tea consumption and chemopreventive effects against skin, lung, breast, colon, liver, stomach, and prostate cancers (Yang, C. S. et al. 2002; Landis-Piwowar et al. 2007). The various polyphenolic catechins contained in green tea are thought to contribute to its chemoprevention activity.

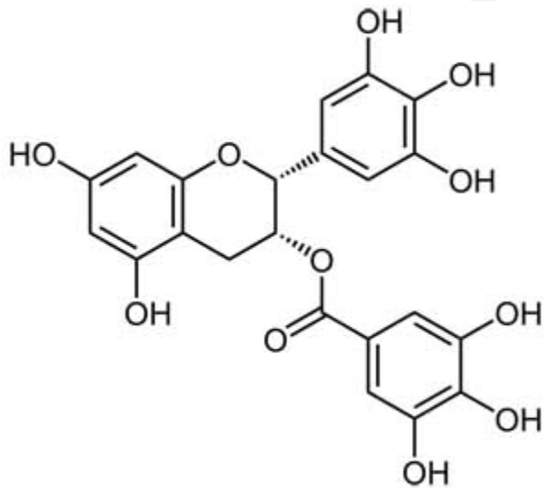


Fig. 3. Chemical structure of EGCG

In particular, numerous studies indicate that EGCG (Figure 3), the most abundant catechin in green tea, is the primary component for these activities (Fujiki 1999; Nagle et al. 2006). *In vitro* and *in vivo* studies have shown that EGCG modulates a wide array of molecular pathways, resulting in induction of apoptosis and cell cycle arrest, and inhibition of invasion, angiogenesis, and metastasis (Shankar et al. 2007; Shankar et al. 2008).

Some studies have found that EGCG may directly or indirectly affect CSC self-renewal pathways. The basal NF-κB activity and ATP- or IL-1β induced activation of NF-κB were negatively regulated by EGCG (Ahmad et al. 2000; Afaq et al. 2003; Guo, S. et al. 2006; Kim, S. J. et al. 2007; Sarkar et al. 2009). EGCG suppressed Akt activation in both colon cancer cell lines and *in vivo* mouse models (Ju et al. 2005; Shimizu et al. 2005; Peng et al. 2006; Bose et al. 2007). In our previous study, EGCG was shown to inhibit the chaperoning function of Hsp90 by impairing the interaction between Hsp90 with its co-chaperones in pancreatic cancer cells, thereby down-regulating Hsp90 client proteins including Akt (Li et al. 2009). EGCG blocked Wnt signaling by stabilizing mRNA of HBP1, a suppressor of Wnt signaling, thereby reducing breast cancer cell tumorigenic proliferation as well as invasiveness (Kim, J. et al. 2006; Kawasaki et al. 2008). The nuclear import of β-catenin was decreased in adenomas isolated from EGCG-treated $Apc^{Min/+}$ mice, a widely used transgenic model recapitulating human colon cancer that bears an Adenomatous Polyposis Coli (APC) gene mutation (Ju et al. 2005; Bose et al. 2007).

Combination of EGCG and doxorubicin was suggested to eradicate putative prostate CSCs ($CD44^+$) (Stearns et al. 2010). EGCG (30 and 60 μM), either alone or in combination with doxorubicin, reduced the colony-forming capability of human prostate cancer cell line PC-3ML. Relatively low dose of EGCG (57 mg/kg) in combination with nontoxic, sub-therapeutic dosages of doxorubicin can eradicate established prostate tumors derived from $CD44^{high}$ tumor-initiating cells isolated from PCa-20a cells in NOD/SCID mice.

Tang et al. have shown that EGCG either alone or in combination with quercetin can eliminate prostate CSC characteristics (Tang et al. 2010). EGCG inhibited the growth and self-renewal capacity of $CD44^+CD133^+$ CSCs contained in human prostate cancer cell lines and $CD44^+\alpha2\beta1^+CD133^+$ CSCs isolated from human primary prostate tumors, as measured by spheroid and colony formation assay. They also suggested that EGCG was able to induce apoptosis in prostate CSCs. In addition, EGCG was found to suppress EMT by inhibiting the expression of vimentin and nuclear β-catenin, as well as the transcription factors slug and snail which are required for EMT induction. The inhibition of EMT markers by EGCG could retard early metastasis of prostate CSCs.

## 6. Quercetin

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) (Figure 4) is a ubiquitous plant polyphenol, naturally occurring in most edible fruits and vegetables, with the high levels being found in apples, cranberries, and blueberries (Androutsopoulos et al. 2010; Guo, W. et al. 2009). Many studies have demonstrated that quercetin possess anti-oxidant, anti-inflammatory and anti-cancer activities (Williamson and Manach 2005; Guo, W. et al. 2009). Quercetin has also been shown to enhance the anti-cancer effects of several chemotherapeutic drugs (Borska et al. 2010; Du et al. 2010; Shih et al. 2010; Wong and Chiu 2010; Limtrakul et al. 2005; Du et al. 2009).

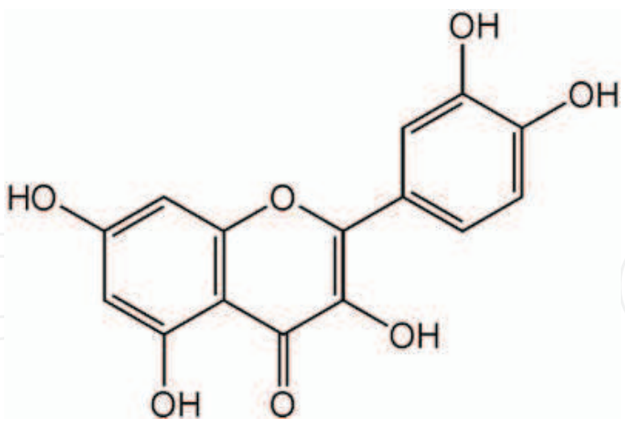


Fig. 4. Chemical structure of quercetin

Several studies have indicated that quercetin may modulate self-renewal pathways. Quercetin was suggested to be a potent inhibitor of β-catenin/TCF signaling in SW480 colon cancer cells, and the reduced β-catenin/TCF transcriptional activity was due to the decreased nuclear β-catenin and TCF-4 proteins (Park, C. H. et al. 2005). The inhibition of colon cancer cell growth by quercetin was related to the inhibition of cyclin D1 and surviving expression through Wnt/β-catenin signaling pathway (Shan et al. 2009).

Zhou et al. demonstrated that quercetin (100-400 μM) mediated reduction of self-renewal capacity of pancreatic CSCs, decreased ALDH1 activity, overcame apoptosis resistance of pancreatic CSCs ($CD44^+CD24^-$), and diminished the expression of proteins involved in the EMT (vimentin and Twist-2) in $CSC^{high}$ cells (Zhou, W. et al. 2010). Quercetin strongly reduced rapid growth of CSC-enriched xenografts, while no toxic side effects were observed (Zhou, W. et al. 2010). They further demonstrated that combination of quercetin with sulforaphane led to a synergistic reduction in self-renewal capacity and a complete abrogation of tumor growth in xenograft mouse model. Similarly, in another recent study, quercetin enhanced the inhibitory effects of sulforaphane on self-renewal capacity of pancreatic CSCs ($CD44^+CD24^+ESA^+$) (Srivastava et al. 2011). Moreover, quercetin (20 μM) was found to synergize with green tea EGCG in inhibiting prostate CSCs (Tang et al. 2010). Quercetin not only potentiated the inhibitory effects of EGCG on self-renewal, migration and invasion capacities of prostate CSCs isolated from primary tumors, but also synergized with EGCG to induce apoptosis (Tang et al. 2010).

| Natural Dietary Compound | Food Origins | Cancer Stem Cells | Potential Molecular Targets |
|---|---|---|---|
| **Sulforaphane** | Cruciferous vegetables | Pancreatic cancer<br>Breast cancer | Wnt/β-catenin; NF-κB binding; EMT markers; Notch-1 |
| **Curcumin** | Turmeric | Breast cancer<br>Brain tumor | Wnt/β-catenin; Gli1 and Ptch1B |
| **EGCG** | Green tea | Prostate cancer | β-catenin; EMT markers; slug and snail |
| **Quercetin** | Ubiquitous, e.g., apple, cranberry, blueberry | Pancreatic cancer<br>Prostate cancer<br>Lung cancer | EMT markers |
| **Piperine** | Black and long pepper | Breast cancer | Wnt/β-catenin; NF-κB |
| **Genistein** | Soy | | GSK3β, β-catenin, Wnt-5a; Notch-2 |
| **Resveratrol** | Grapes, berries, plums, and peanuts | | β-catenin, GSK3β; Notch-1 |
| **Lycopene** | Tomatoes, watermelon, papaya, pink grapefruit | | β-catenin |
| **Vitamin D3** | Fish, egg yolk, beef liver | | TCF-4, E-cadherin |

Table 1. Natural dietary components that potentially regulate self-renewal pathways and inhibit CSCs

## 7. Conclusion

Naturally-occurring dietary components are advantageous in several aspects as chemoprevention agents: (1) they are present in commonly consumed food, which is readily available to most people in daily life; (2) they usually have very low or no toxicity, in contrast to most chemotherapy drugs; (3) many of these compounds have shown potential as an adjunct to chemotherapy drugs in some clinical trials. Although the reports were very limited for dietary components to inhibit CSCs, many of them have been shown to be directly or indirectly involved in modulation of CSC self-renewal pathways. All of these studies stress the need for investigating the efficacy of dietary components against CSCs and elucidating the mechanisms of action. In Table 1, we summarize the compounds discussed in this chapter as well as some others dietary components that may affect the element(s) of self-renewal pathways.

Since CSCs are more resistant to conventional therapies in comparison with differentiated cells constituting the tumor bulk, these studies will provide strong rationale for preclinical and clinical evaluation of the dietary components or potentially their native food extracts combined with chemotherapy. Combination of dietary intervention that are directed against CSCs and conventional chemotherapy would have the potential to eliminate CSCs, overcome tumor resistance, reduce recurrence, and eventually improve patient survival.

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**Cancer Stem Cells - The Cutting Edge**

Edited by Prof. Stanley Shostak

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Over the last thirty years, the foremost inspiration for research on metastasis, cancer recurrence, and increased resistance to chemo- and radiotherapy has been the notion of cancer stem cells.The twenty-eight chapters assembled in Cancer Stem Cells - The Cutting Edge summarize the work of cancer researchers and oncologists at leading universities and hospitals around the world on every aspect of cancer stem cells, from theory and models to specific applications (glioma), from laboratory research on signal pathways to clinical trials of bio-therapies using a host of devices, from solutions to laboratory problems to speculation on cancersâ€™ stem cellsâ€™ evolution. Cancer stem cells may or may not be a subset of slowly dividing cancer cells that both disseminate cancers and defy oncotoxic drugs and radiation directed at rapidly dividing bulk cancer cells, but research on cancer stem cells has paid dividends for cancer prevention, detection, targeted treatment, and improved prognosis.

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