Flavonoids Targeting CSC

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Cancer stem cells (CSC) have been identified in several types of solid tumors. In some cases, CSC may be the source of all the tumor cells, the cause of the tumor's resistance to chemotherapeutic agents, and the source of metastatic cells. Thus, a combination therapy targeting non-CSC tumor cells as well as specifically targeting CSCs holds the potential to be highly effective. Natural products (NPs) have been a historically rich source of biologically active compounds and are known for their ability to influence multiple signaling pathways simultaneously with negligible side effects. Natural flavonoids or potent derivatives are good candidates in exhibiting anti-CSC activity and targeting key functions required for CSC survival.

natural products cancer stem cells cancer therapy flavonoids

1. Flavonoids Targeting Cancer Stem Cells (CSC)

Flavonoids are dietary polyphenols present in a wide variety of plants, fruits, vegetables, nuts, and teas [1]. More than 6000 flavonoids were isolated, identified, and divided into subclasses such as flavones, flavonols, flavanols, isoflavones, and isoflavans [2][3]. Quercetin and Kaempferol are the most prominent flavonols in foods, Luteolin and Apigenin are prominent flavones, Genistein and Daidzein are the prominent isoflavones present in soybeans, and catechins are the most prominent constituents of green teas [4]. Flavonoids have been of high scientific interest since the 1990s due to their beneficial effects on human health. Consuming flavonoids may contribute to preventing cardiovascular and neurodegenerative diseases and cancer [5][6]. Recently, there is growing evidence of the preventive effect of flavonoids on cancer stem cells [7][8].

Quercetin: Quercetin is a flavonol found in various plant-based foods. Quercetin exhibits anticancer properties both in vivo and in vitro [9], and may exert its anticancer effect through several mechanisms, including suppressing inflammation, inducing apoptosis, acting as an antioxidant, and modulating signaling pathways [10][11]. Cao et al. have studied the effect of quercetin on pancreatic cancer stem-like cells using human pancreatic cancer cell lines. It was found that quercetin inhibited the expression of CSC cell surface markers CD24 and CD133 in pancreatic cancer stem-like cells, and induced pancreatic CSCs differentiation mediated by altered function of β-catenin, a signal transduction pathway which plays an important role in maintenance and progression of pancreatic cancer [12][13].

Erdogan et al. described the effect of quercetin on prostate cancer stem cells (PCSCs) survival and migration. The authors examined the effect of quercetin on CD44+/CD133+ and CD44+ stem cells isolated from prostate cancer cells (PC3 and LNCaP cells, respectively). Quercetin inhibited the survival of PC3 and CD44+/CD133+ in a dose-

and time-dependent manner. Midkine (MK) is a multifunctional heparin-binding cytokine with anti-apoptotic, migration-promoting, angiogenic, and other biological functions [14][15]. Administration of quercetin to MK-knockout cells resulted in a higher inhibition of cell proliferation compared with quercetin and MK siRNA alone in both androgen-insensitive and androgen-sensitive cells. The combination of quercetin and MK siRNA could significantly promote apoptosis and inhibit migration of PC3 and CD44+/CD133+ cells via downregulating the expression of PI3K/PTEN, MAPK, and NF-κB signaling pathways [16][17]. Tsai et al. used the prostate cancer stem cells DU145-III isolated from DU145 prostate tumor cell line (DU145-P) to explore the effect of quercetin on prostate cancer stem cells. Quercetin suppressed the migratory and invasive potential and vasculogenic mimicry (VM) in DU145-III cells. It lowered the expression of CSC markers CD44, ABCG2, Sox2, and Nanog, attenuated cancer stem cell-associated spheroid formation, and inhibited the JNK signaling pathway [18]. Wei et al. also examined the inhibition effect of quercetin on the self-renewal of breast cancer stem cells (BCSCs), using mammosphere formation assay in human AS-B145 and ASB244 cells. Quercetin suppressed the size and number of primary and secondary mammospheres in a dose-dependent matter. The same results were obtained using Sca-1+4T1 mouse BCSCs [19].

By using human gastric cancer stem cells (GCSCs) isolated from MGC803, a human gastric cancer cell line, Shen et al. showed that quercetin inhibited GCSC survival by inducing cell mitochondrial-dependent apoptosis through the inhibition of PI3K/Akt signaling [20]. The effect of quercetin on cancer multidrug resistance (MDR) was also evaluated. Li et al. used doxorubicin (Dox)-resistant human breast cancer MCF-7/dox cells to examine the effect of quercetin on MDR reversal and investigate its possible mechanism. In this study, quercetin eliminated BCSC and reversed the MDR in breast cancer cells [21].

In another study, Cao et al. showed that quercetin treatment can overcome pancreatic cancer cell resistance to chemotherapeutic drugs such as gemcitabine [12] by exhibiting significant synergy with the standard chemotherapy drugs and reverse MDR. Moreover, Slusarz et al. identified quercetin as an inhibitor of the hedgehog signaling pathway, implicated in cancer stem biology, in prostate cancer [22].

Luteolin: Luteolin (LU) is a flavone found in more than 300 plant species, many of which are available in the human diet [23]. Like quercetin, luteolin was found to suppress CSCs properties and metastasis in the isolated PCSCs, Du145-III [18]. Moreover, luteolin suppressed EMT and cell migration in triple negative cancer cells [24]. Ma et al. reported that luteolin inhibited the survival and self-renewal of liver cancer stem-like cells. Luteolin was also able to affect the number and size of the tumor spheroids [25].

Using human breast cancer xenograft tumors in nude mice, Cook et al. have shown that luteolin reduced breast cancer cell viability, xenograft tumor VEGF expression, and blood vessel density. Furthermore, luteolin blocked MPA-induced acquisition of stem cell-like properties by breast cancer cells. It was also shown that luteolin inhibited various stem cell markers such as CD44, ALDH1, and others in breast cancer cells [26][27][28].

Tu et al. have investigated the effect of luteolin on oral cancer stem cells (OCSCs) using normal human gingival epithelioid S g cells and OCSC cell lines. Luteolin effectively inhibited the proliferation rate, self-renewal, aldehyde dehydrogenase 1 activity, and CD44 positivity of OCSC by the inactivation of IL-6/STAT3 signaling. Luteolin

restored radio-sensitivity in OCSC. The combination between luteolin and radiation treatment showed a synergistic effect on invasiveness and clonogenicity of OCSC. Interestingly, luteolin did not cause significant cytotoxicity in normal epithelial cells [29].

Chakrabarti et al. showed that luteolin and silibinin have a synergetic effect on the inhibition of glioblastoma stem cells (GbSC). Their study demonstrated that a combination of luteolin and silibinin effectively inhibited proliferation, migration and invasion and induced apoptosis through downregulation of PKCα and iNOS in human glioblastoma SNB19 cells and GbSC cells [30].

Apigenin: Apigenin is a flavone commonly found in plant-derived beverages, some herbs, fruits, and many vegetables, such as parsley, tea, and thyme, and has anticancer properties [31][32].

Erdogan et al. examined the effect of apigenin on prostate CSCs (CD44+) isolated from human prostate cancer cells (PC3). Apigenin inhibited PCSCs and PC3 cell survival and migration in a dose-dependent manner, induced apoptosis via an extrinsic caspase-dependent pathway, and reduced pluripotency marker Oct3/4 protein expression, which may be associated with the downregulation of PI3K/Akt/NF-κB signaling [33].

Ketkaew et al. used the head and neck squamous cell carcinoma cell line HN-30 to examine the effect of apigenin on squamous CSCs. HN-30 cells show expression of stem cell markers induced by hypoxia. Apigenin significantly decreased HN-30 cell viability in a dose- and time-dependent manner and significantly downregulated the expression of CD44, NANOG, and CD105 markers [34].

Kim et al. investigated the effect of apigenin on cancer stem cell-like phenotypes of human glioblastoma (GBM) cell lines U87MG and U373MG. Apigenin inhibited the self-renewal capacity, cell growth, and clonogenicity, and also the invasiveness of GBM stem-like cells. Apigenin inhibited the GBM stem cell-like phenotypes via downregulation of the c-Met signaling pathway. It blocked the phosphorylation of c-Met and its downstream effectors and reduced the expression levels of stem cell markers such as CD133, Nanog, and Sox2 [35].

Apigenin was also reported to sensitize human CD44+ prostate cancer stem cells to cisplatin therapy by inhibition of cancer stem cells of the lung [36]. The combination of apigenin and cisplatin significantly enhanced cisplatin's cytotoxic and apoptotic effects through downregulation of Bcl-2. The combined therapy suppressed the phosphorylation of PI3K and Akt, inhibited the protein expression of NF-κB, and downregulated the cell cycle by upregulating p21, as well as cyclin-dependent kinases CDK-2, -4, and -6. Apigenin also increased the inhibitory effects of cisplatin on cell migration via downregulation of Snail expression [36][37].

Other Flavonoids that Affect CSC: Wogonin is an O-methylated flavone with anticancer properties found in *Scutellaria baicalensis* [38]. It is a well-known drug used for various types of cancers, including hepatic carcinoma, pulmonary carcinoma, and glioblastoma. Wogonin induces apoptosis in the CSCs of human osteosarcoma cells (CD133-positive osteosarcoma cells), inhibits its mobility in vitro via downregulation of MMP-9 expression, and represses its self-renewal ability [39]. Furthermore, an in vitro study revealed that wogonin exhibits

an inhibitory function against osteosarcoma stem cells. Wogonin suppressed the expression of stem cell-related genes by regulating reactive oxygen species (ROS) levels and ROS-related signaling [40].

Genistein is a naturally occurring isoflavone, which suppressed tumorsphere formation and decreased Gli1 and CD44 expression [41]. In xenograft models, genistein inhibited tumor growth and downregulated the expression of Gli1 and CD44 in tumor tissues in docetaxel-resistant prostate cancer cells [41] and in a breast cancer model [42]

Myricetin is a flavonol found in berries, onions, and red grapes. Myricetin promotes osteogenic differentiation of human periodontal ligament stem cells via the upregulation of alkaline phosphatase (ALP) activity and expression of osteogenic-related factors through BMP-2/Smad and ERK/JNK/p38 MAPK pathways [43].

Epigallocatechin gallate (EGCG), found in tea leaves, was found to inhibit the self-renewal capacity of human PCSC of the CD44+CD133+ population. EGCG induced apoptosis by activating caspase-3/7 and inhibiting the expression of Bcl-2, survivin, and XIAP in CSCs and inhibited CSC's migration and invasion. Interestingly, EGCG synergizes with quercetin in eliminating cancer stem cell-characteristics [44][45]. Moreover, EGCG was found to downregulate the expression of Gli1 and inhibit the proliferation of a number of cancer cell types [22][46]. EGCG inhibited cellular self-renewal capacity through regulating stem cell markers, Nanog, c-Myc and Oct4, as well as Hh signaling mediators, Smo, Ptch and Gli1/2 [47]. In an animal model of carcinogen-induced liver cancer, EGCG reduced the population of CD44-positive cells and inhibited the expression of Gli1, Smo, cyclin D1, cMyc, and EGFR [48].

Fisetin is a flavonol that is naturally abundant in many fruits and vegetables and has anti-tumor properties [49][50]. Si et al. examined its effect on human renal CSC (HuRCSC) isolated from renal cancer samples and found that fisetin inhibited the proliferation by an epigenetic mechanism. It significantly decreased the expression of ten-eleven translocation protein1 (TET1), effectively inhibited the 5−hydroxymethylcytosine (5hmC) modification levels at the CpG islands in cyclin Y (CCNY) and CDK16, and reduced their transcription and activity, which caused a cell cycle arrest [51].

Tabasum et al. explored fisetin anti-metastatic effects in non-small cell lung carcinoma (NSCLC) cell lines A549 and H1299 with emphasis on epithelial to mesenchymal transition (EMT). EMT promotes metastasis by allowing the tumor cells to acquire increased migratory and invasive properties, mediating their dissemination to faraway sites [52][53]. It was found that fisetin significantly inhibited the migration and invasion of NSCLC cells under non-cytotoxic concentrations. Fisetin attenuated EMT in both cell lines with upregulated expression of epithelial markers and downregulation of mesenchymal markers. Furthermore, fisetin treatment downregulated NSCLC stem cell signature markers CD44 and CD133. Thus, fisetin is a potential therapeutic agent for lung cancer stem cells [54].

Broussoflavonol B from the bark of the Paper Mulberry tree (*broussonetia papyrifera*), exhibited potent growth inhibitory activity towards breast cancer cells, sensitized breast cancer stem/progenitor cells to tamoxifen, and restricted the proliferation of ER-negative breast cancer stem-like cells [55].

Morusin, a butenylated flavonoid isolated from the root bark of Moraceae, also has the potential to target cervical CSCs by attenuating NF-kB activity [56].

Icaritin a prenylflavonoid derivative from Epimedium Genus, inhibited growth of hepatic cancer stem cells through downregulating STAT activation [57] and inhibited malignant growth of hepatocellular carcinoma-initiating cells (HCICs) [58]. Its analogue SNG1153 inhibited tumorsphere formation and decreased CD133-positive (lung CSC marker) cancer cells. It also inhibited the growth of lung CSCs, which may be a novel therapeutic agent to treat human lung cancer. SNG1153 induced β-catenin phosphorylation and downregulated β-catenin [59].

Casticin, which is derived from *Fructus Viticis Simplicifoliae*, inhibited the self-renewal of liver cancer stem cells from the MHCC97 cell line, and β-catenin was identified as the potential target [60].

2. Flavonoids Targeting ABCG2 in CSCs

ABC transporters consist of 49 transporter proteins that are classified into seven subfamilies, ABCA to ABCG, that locate in the cell membrane and have diverse functions [61]. By using ATP, ABC transporters work to transport their substrates across the cell membrane and to protect cells against xenobiotics, including some anti-cancer drugs [62].

Cancer stem cells are known to express elevated levels of ABCG2 and consequently are characterized with multi-drug chemoresistance [63]. These cells are thought to lead to a relapse after chemotherapy. Therefore, inhibition of ABCG2 could have an additional benefit besides counteracting multidrug resistance, selective killing of CSC. Interestingly, an increasing number of FDA-approved tyrosine kinase inhibitors (TKIs), including imatinib and gefitinib, reported to downregulate or inactivate ABCG2 [64] and, therefore, may serve as candidates to reverse cancer stem cell chemoresistance. Similarly, a number of natural products were also reported to inactivate ABCG2 and thus sensitize cancer stem cells to activity of standard chemotherapy including estrogenic compounds; several tamoxifen derivatives in addition to phytoestrogens and flavonoids have been shown to reverse ABCG2-mediated drug resistance. Flavonoids seem promising ABCG2 inhibitors, as they exhibit selective and broad-spectrum activity [65].

The flavonoids silymarin, hesperetin, quercetin, and daidzein were shown to increase the intracellular accumulation of mitoxantrone in ABCG2-expressing cells [66]. Flavonoids such as Chrysin and biochanin A reported as potent inhibitors of ABCG2 in breast cancer cells, and were consequently able to sensitize breast cancer stem cells to cancer chemotherapy activity such as mitoxantrone [67]. Interestingly, inhibitory flavonoids appear either non-competitive or partially competitive towards mitoxantrone efflux. Most compounds do not inhibit ATPase activity in ABCG2, and are assumed not to be transported themselves by the transporter.

Structure activity studies led to the identification of novel ABCG2 inhibitors such as 6-prenylchrysin [68] exhibiting an IC_{50} of 0.3 M. The relatively low toxicity of 6-prenylchrysin and efficient sensitization of cell growth to mitoxantrone made these compounds promising for future potential use in clinical trials.

In a recent study, the inhibitory effect of naturally occurring flavonoids on ABCG2 was correlated with their positive effects on the pharmacokinetics of anticancer drugs [69]. A panel of 32 flavonoids was screened by using topotecan accumulation and cytotoxicity assays, and led to the identification of 3′,4′,7-trimethoxyflavone as the most potent inhibitors of ABCG2.

It was found that multiple flavonoid combinations induce strong ABCG2 inhibition by increasing both accumulation and cytotoxicity of mitoxanthrone in ABCG2-overexpressing breast cancer cells. The best candidates were biochanin A (isoflavone), kaempferide (flavonol), 5,7-dimethoxyflavone and 8-methylflavone [70].

Chalcones, which also belong to the flavonoids family and are natural compounds present in edible plants, were found to inhibit differentially ABCB1 and ABCG2, basic chalcones being more efficient on ABCB1 transporter [71] and non-basic chalcones on the ABCG2 transporters [72]. Chalcones exhibiting the highest activity and selectivity toward ABCG2 were found among derivatives which are dimethoxylated or dihydroxylated at the A-ring, as evidenced by the mitoxantrone accumulation and cytotoxicity assays.

3. Anti-CSC Activity of Flavonoids Mediated by Modulation of microRNAs

MicroRNAs (miRNAs) are short (~17–28 nucleotides) endogenous RNA molecules which regulate mRNA stability and translation as part of the RISC complex, by binding to specific sites in the 3′ untranslated regions of the mRNAs through partial sequence complementarity [73]. Since the discovery of miRNAs at the turn of the century, their involvement in a variety of biological processes has been described, and it is estimated that the expression of >60% of all protein-coding genes is regulated by miRNAs [74], and depending on the inclusion criteria, between 600 and 2000 miRNAs are encoded in the human genome [75][76].

One of the better studied contexts of miRNA function has been the biology of cancer. A panel of miRNAs has been found to be upregulated in various types of cancer, with their higher levels contributing to the different aspects of oncogenesis (thus, they were dubbed “oncomiRs”) [77]. Other miRNAs have been identified as downregulated in cancer and function as tumor suppressors [78]. Finally, some miRNAs (such as miR-10b and miR-221/222) can function as both tumor suppressors and oncomiRs, based on the cancer type and stage, and depending on the specific selection and repertoire of expressed target genes [79][80][81][82].

A number of miRNAs have been shown to function in the maintenance of cancer stem cells (CSC) [83]. Thus, the miR-34, miR-199, and miR-200 families, as well as miR-1, miR-143 and miR-146 have all been shown to regulate elements of the Notch pathway, which plays a central role in CSC [84]. Other miRNAs have been implicated in the regulation of EMT, among them miR-106b, miR-22, and miR-203. miR-9/9* and miR-21 have been reported to promote the CSC phenotype, whereas miR-10b, miR-328 and miR-495 have been shown to promote metastasis and drug resistance of the cells. The Let-7 family and miR-302 have been reported as involved in CSC differentiation (review, [85]). Additionally, several tumor suppressors (e.g., let-7, miR-34, miR-146, miR-200) and

oncomiRs (e.g., miR-21, miR-210) are involved in reactive oxygen species signaling, which may induce CSC properties and EMT (review, [86][87]).

Several known tumor suppressor miRNAs are direct regulators of the expression of CSC marker proteins. Thus, based on the TargetScan prediction algorithm [88], the PROM1 gene encoding the CD133 peptide has a conserved miR-200 binding site in its 3′UTR, and the targeting was validated in a rat hepatic oval cell model [89]. Similarly, CD44 was reported to be directly regulated by miR-221/222 in bone marrow cells [90].

Effects of Flavonoids on Micrornas: Several studies have examined the effects of flavonoid exposure on the levels of specific miRNAs and their downstream targets. Thus, the Koike group has reported that treatment with the flavonoid apigenin suppresses the exogenous overexpression of miR-103 in mice, resulting in improved glucose tolerance [85]. The same group has also reported that apigenin treatment suppresses miR-122 levels in vitro, likely via a mechanism involving TRBP phosphorylation [87]. Although that particular study was focused on the role of miR-122 in HCV infection, a tumor suppressor role has previously been reported for this miRNA [91][92].

The ability of flavonoids to affect miRNAs involved in carcinogenesis (review, [93][94]) is particularly relevant in CSCs. Thus, in breast cancer cells, exposure to Glabridin, a phytochemical from the root of Glycyrrhiza glabra, upregulated miR-148a via promoter de-methylation, leading to the suppression of SMAD2 and decrease in CSC-like properties [95]. This attenuation was observed both in vitro, i.e., in MDA-MB-231 and Hs-578T breast cancer cell lines, and in mouse xenograft models. The upregulation of miR-148 in breast cancer cell lines by Glabridin also suppressed the Wnt/β-catenin signaling pathway, resulting in decreased angiogenesis [96].

In non-small-cell lung cancer, EGCG, enhanced the levels of mir-485-5p, suppressing the levels of two oncogenic targets, CD44 and the nuclear receptor RXRα, both effects contributing to the decrease in CSC-like properties [97] [98]. Inhibitors of miR-485 increased CSC-like phenotypes, which could be reversed by indicated doses of EGCG [98]; this link was also tested in vivo. Finally, in pancreatic duct carcinoma cell lines, a combination of sulforaphane, quercetin and catechin treatments (including EGCG) led to the upregulation of the miRNA let-7 and a decrease in the CSC-like self-renewal properties [99]. Quercetin also induced miR-200b-3p, decreasing Notch signaling, promoting daughter cell asymmetry and inhibiting the self-renewal in pancreatic cancer cells [100].

In CD133+ melanoma cells, Morin treatment induced miR-216a. When carried out in vitro, this led to a reduction in cell viability, in sphere formation, and in the expression of stem cell marker genes CD20, CD44, CD133 and Wnt-3A. This was also observed in vivo: a melanoma xenograft model treated by Morin showed reduced tumor size and weight, as well as reduced expression of stem cell markers and Wnt-3A [101].

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