2022-8 Cancer Stem Cells (CSCs)

Herbs have many ingredients that work together to support a person's health, and they have been consumed for thousands of years by billions of people in China, India and many other countries. Some of these herbal foods are now classified as adaptogens. Adaptogens, by definition, do not have an active ingredient, but their ingredients work together to help the body handle mental and physical stress.

With the discovery of apoptosis pathways, scientists are using cancer tissue culture apoptosis screens on herbs, mushrooms and other plants to help find possible ingredients to chemically modify into new patentable drugs.

However, most, if not all, of these food bioactive compounds are bitter, acrid, or astringent and therefore aversive to the consumer. Some have long been viewed as plant-based toxins. As a result, the food industry routinely removes these compounds from plant foods through selective breeding and a variety of debittering processes. See the last abstract below.

Every day, the average healthy person removes 60,000,000,000 defective cells by apoptosis, self-digestion. Many diseases happen because defective cell are not fixed or removed. Apoptosis pathways are naturally activated by the bitter, acrid, or astringent food ingredients removed from our food.

For example, a disease can happen when aberrant or defective cells are not removed or repaired and allowed to grow. In the past, the bitter, acrid, or astringent ingredients in food activated apoptosis pathways every day in healthy people to keep them healthy and free of disease.

Emerging evidence supports the presence of a unique population of cells called cancer stem cells (CSCs) as potential cancer inducing cells, and efforts are underway to develop therapeutic strategies targeting these cells. To overcome this problem, we need novel preventive agents that target these CSCs. Natural compounds or

phytochemicals have the ability to target these CSCs and their signaling pathways.

The father of medicine, Hippocrates, said, "Let your food be your medicine and your medicine be your food."

A Sample of Cancer Stem Cell Studies in PubMed

268 Articles on 9Nov2021

Review
Phytother Res
actions:
. 2021 Jul;35(7):3649-3664. doi: 10.1002/ptr.7059. Epub 2021 Feb 22.

Epigenetic targeting of cancer stem cells by polyphenols (cancer stem cells targeting)

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• PMID: 33619811 DOI: 10.1002/ptr.7059

Abstract

Epigenetic alterations are one of the main factors that disrupt the expression of genes and consequently, they have an important role in the carcinogenicity and the progression of different cancers. **Cancer stem cells (CSCs) are accountable for the recurrence, metastasis, and therapeutic failure of cancer. The noticeable and specific pathways in CSCs can be organized by epigenetic mechanisms such as DNA methylation, chromatin remodeling, regulatory RNAs, among others. Since epigenetics modifications can be changed and reversed, it is a possible tool for cancer control and treatment. Epigenetic therapies against CSCs are emerging as a very new strategy with a good future expectation to treat cancer patients. Phenolic compounds are a vast group of substances with anticarcinogenic functions, antiinflammatory, and antioxidative activities. It seems these**

characteristics are related to neutralizing CSCs development, their microenvironment, and metabolism through epigenetic mechanisms. In the current work, the types of epigenetic changes known in these cells are introduced. In addition, some studies about the use of polyphenols acting through a variety of epigenetic mechanisms to counteract these cells will be reviewed. **The reported results seem to indicate that the use of these phenolic compounds may be useful for CSCs defeat.**

Keywords: cancer stem cells (CSCs); epigenetics; polyphenols.

Review
Int J Mol Sci
actions: 2020 Jan 8;21(2):401. doi: 10.3390/ijms21020401.

Alleviation of Multidrug Resistance by Flavonoid and Non-Flavonoid Compounds in Breast, Lung, Colorectal and Prostate Cancer

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• PMID: 31936346 PMCID: PMC7013436 DOI: 10.3390/ijms21020401
Free PMC article

Abstract

The aim of the manuscript is to discuss the influence of plant polyphenols in overcoming multidrug resistance in four types of solid cancers (breast, colorectal, lung and prostate cancer). Effective treatment requires the use of multiple toxic chemotherapeutic drugs with different properties and targets. However, a major cause of cancer treatment failure and metastasis is the development of multidrug resistance. Potential mechanisms of multidrug resistance include increase of drug efflux, drug inactivation, detoxification mechanisms, modification of drug target, inhibition of cell death,

involvement of cancer stem cells, dysregulation of miRNAs activity, epigenetic variations, imbalance of DNA damage/repair processes, tumor heterogeneity, tumor microenvironment, epithelial to mesenchymal transition and modulation of reactive oxygen species. Taking into consideration that synthetic multidrug resistance agents have failed to demonstrate significant survival benefits in patients with different types of cancer, recent research have focused on beneficial effects of natural compounds. Several phenolic compounds (flavones, phenolcarboxylic acids, ellagitannins, stilbens, lignans, curcumin, etc.) act as chemopreventive agents due to their antioxidant capacity, inhibition of proliferation, survival, angiogenesis, and metastasis, modulation of immune and inflammatory responses or inactivation of pro-carcinogens. Moreover, preclinical and clinical studies revealed that these compounds prevent multidrug resistance in cancer by modulating different pathways. Additional research is needed regarding the role of phenolic compounds in the prevention of multidrug resistance in different types of cancer.

Keywords: chemoresistance; malignancy; phenolic compounds.

Review
Curr Med Chem
actions:
. 2018;25(22):2585-2594. doi: 10.2174/0929867324666170127095832.

Targeting Cancer Stem Cells for Chemoprevention of Pancreatic Cancer

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- PMID: 28137215 PMCID: PMC5630517 DOI: 10.2174/0929867324666170127095832

Free PMC article

Abstract

Pancreatic ductal adenocarcinoma is one of the deadliest cancers worldwide and the fourth leading cause of cancer-related deaths in United States. Regardless of the advances in molecular pathogenesis and consequential efforts to suppress the disease, this cancer remains a major health problem in United States. By 2030, the projection is that pancreatic cancer will be climb up to be the second leading cause of cancer-related deaths in the United States. **Pancreatic cancer is a rapidly invasive and highly metastatic cancer, and does not respond to standard therapies. Emerging evidence supports that the presence of a unique population of cells called cancer stem cells (CSCs) as potential cancer inducing cells and efforts are underway to develop therapeutic strategies targeting these cells. CSCs** are rare quiescent cells, and with the capacity to self-renew through asymmetric/ symmetric cell division, as well as differentiate into various lineages of cells in the cancer. **Studies have been shown that CSCs are highly resistant to standard therapy and also responsible for drug resistance, cancer recurrence and metastasis. To overcome this problem, we need novel preventive agents that target these CSCs. Natural compounds or phytochemicals have ability to target these CSCs and their signaling pathways. Therefore, in the present review article, we summarize our current understanding of pancreatic CSCs and their signaling pathways, and the phytochemicals that target these cells including curcumin, resveratrol, tea polyphenol EGCG (epigallocatechin- 3-gallate), crocetinic acid, sulforaphane, genistein, indole-3-carbinol, vitamin E δ- tocotrienol, Plumbagin, quercetin, triptolide, Licofelene and Quinomycin. These natural compounds or phytochemicals, which inhibit cancer stem cells may prove to be promising agents for the prevention and treatment of pancreatic cancers.**

Keywords: Cancer stem cells; DCLK1; chemoprevention; natural compounds; pancreatic cancer; signaling..

Review
Semin Cancer Biol
actions:
. 2016 Oct;40-41:192-208. doi: 10.1016/j.semcancer.2016.09.001. Epub 2016 Sep 5.

Targeting cancer stem cells and signaling pathways by phytochemicals: Novel approach for breast cancer therapy

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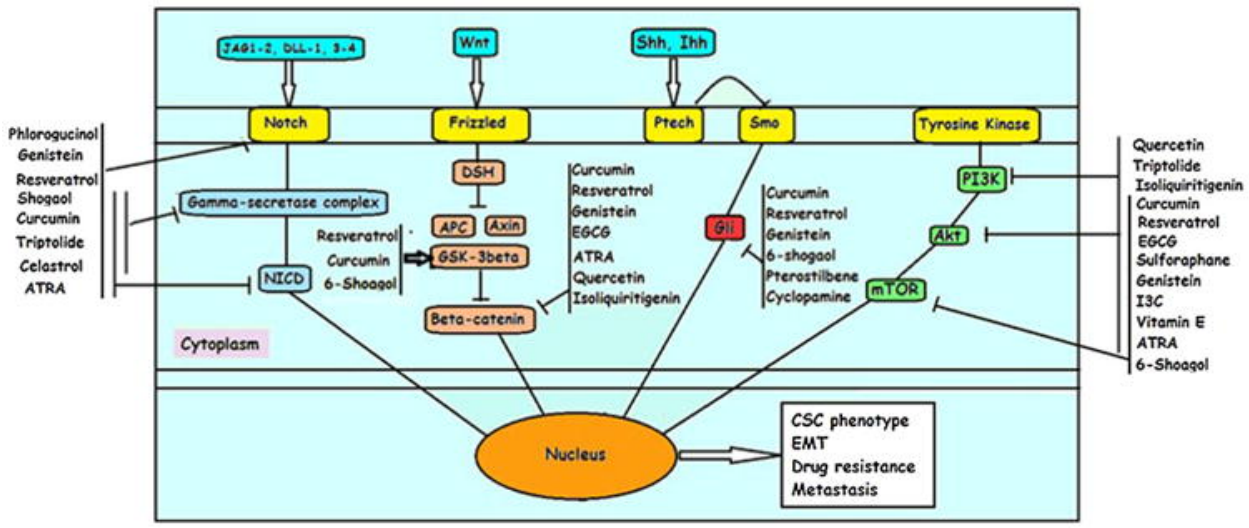
- PMID: 27609747 PMCID: PMC5565737 DOI: 10.1016/j.semcancer.2016.09.001

Abstract

Breast cancer is the most common form of cancer diagnosed in women worldwide and the second leading cause of cancer-related deaths in the USA. **Despite the development of newer diagnostic methods, selective as well as targeted chemotherapies and their combinations, surgery, hormonal therapy, radiotherapy, breast cancer recurrence, metastasis and drug resistance are still the major problems for breast cancer. Emerging evidence suggest the existence of cancer stem cells (CSCs), a population of cells with the capacity to self-renew, differentiate and be capable of initiating and sustaining tumor growth. In addition, CSCs are believed to be responsible for cancer recurrence, anticancer drug resistance, and metastasis.** Hence, compounds targeting breast CSCs may be better therapeutic agents for treating breast cancer and control recurrence and metastasis. **Naturally occurring compounds, mainly phytochemicals have gained immense attention in recent times because of their wide safety profile, ability to target heterogeneous populations of cancer cells as well as CSCs, and their key signaling pathways. Therefore, in the present review article, we summarize our current understanding of breast CSCs and their signaling pathways, and the phytochemicals that affect these cells including curcumin, resveratrol, tea polyphenols (epigallocatechin-3-gallate, epigallocatechin), sulforaphane, genistein,**



indole-3-carbinol, 3, 3'-di-indolylmethane, vitamin E, retinoic acid, quercetin, parthenolide, triptolide, 6-shogaol, pterostilbene, isoliquiritigenin, celastrol, and koenimbin. These phytochemicals may serve as novel therapeutic agents for breast cancer treatment and future leads for drug development.

Keywords: Breast cancer; Cancer stem cells; Curcumin; Phytochemicals; Signaling pathways.

Review
Aging (Albany NY)
actions:
. 2017 Jun 12;9(6):1477-1536. doi: 10.18632/aging.101250.

Effects of resveratrol, curcumin, berberine and other nutraceuticals on aging, cancer development, cancer stem cells and microRNAs

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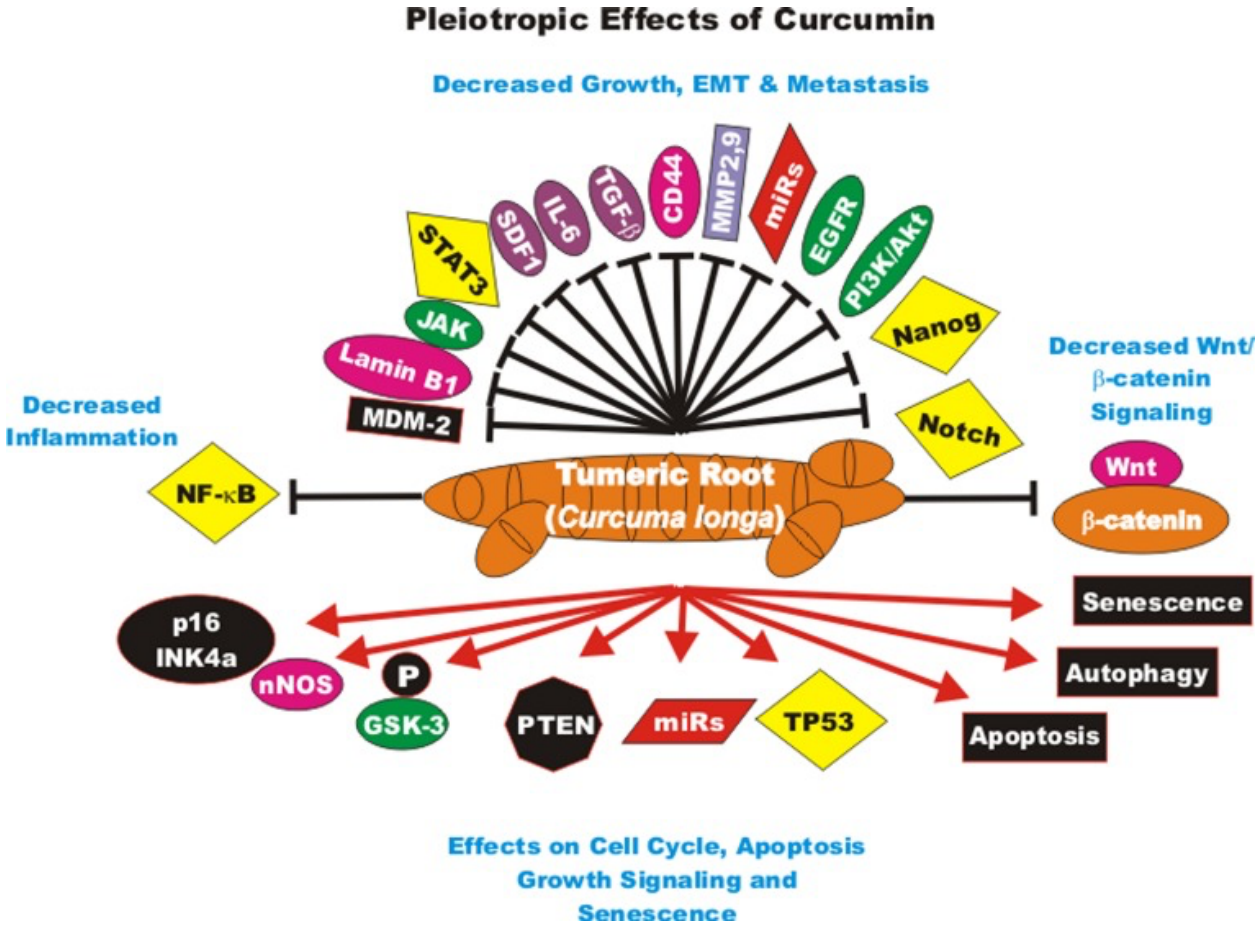
- PMID: 28611316 PMCID: PMC5509453 DOI: 10.18632/aging.101250

Abstract

Natural products or nutraceuticals have been shown to elicit anti-aging, anti-cancer and other health-enhancing effects. A key target of the effects of natural products may be the regulation of microRNA (miR) expression which results in cell death or prevents aging, diabetes, cardiovascular and other diseases. This review will focus on a few natural products, especially on resveratrol (RES), curcumin (CUR) and berberine (BBR). RES is obtained from the skins of grapes



and other fruits and berries. RES may extend human lifespan by activating the sirtuins and SIRT1 molecules. CUR is isolated from the root of turmeric (*Curcuma longa*). CUR is currently used in the treatment of many disorders, especially in those involving an inflammatory process. CUR and modified derivatives have been shown to have potent anti-cancer effects, especially on cancer stem cells (CSC). BBR is also isolated from various plants (*e.g., Coptis chinensis*) and has been used for centuries in traditional medicine to treat diseases such as adult- onset diabetes. Understanding the benefits of

these and other nutraceuticals may result in approaches to improve human health.

Keywords: CSCs; SIRT; curcumin; gene methylation; miRs; natural products; resveratrol.

Conflict of interest statement

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest with publication of this manuscript.

Wild Yam Root Powder, Dioscorea villosa (Contains: Dioscin and Diosgenin)

Cell Death Dis

actions:

. 2018 Mar 1;9(3):343. doi: 10.1038/s41419-018-0363-x.

Dioscin inhibits stem-cell-like properties and tumor growth of osteosarcoma through Akt/GSK3/β-catenin signaling pathway

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- PMID: 29497056 PMCID: PMC5832770 DOI: 10.1038/s41419-018-0363-x

Free PMC article

Full-text links Cite

Abstract

Osteosarcoma is the most common primary bone tumor in children and adolescents. Many patients with osteosarcoma always develop drug resistance to current chemotherapy regimens, which induces a poor prognosis. And cancer stem cells (CSCs) have been reported to possess the properties to self-renew and maintain the phenotype of tumor, which may lead to clinical treatment failure. Thus, it is an urgent task to develop several potentially useful therapeutic agents,

which could target CSCs in osteosarcoma. This study aims to clarify the in vitro and in vivo anti-osteosarcoma effects of dioscin, the primary component derived from Discorea nipponica Makino, and its molecular mechanism of action. In this study, all the ten human osteosarcoma cell lines were sensitive to dioscin treatment in a dose- and time-dependent manner. Dioscin inhibits proliferation and induces cell cycle arrest as well as apoptotic cell death in osteosarcoma cells. More importantly, oral administration of dioscin (60 mg/kg) showed significant therapeutic effect on osteosarcoma growth without obvious side effects in vivo. In addition, dioscin possesses the ability to suppress stem-cell-like phenotype of osteosarcoma cells. Mechanistically, dioscin inhibits osteosarcoma stem-cell-like properties and tumor growth through repression of Akt/GSK3/β-catenin pathway. Moreover, β-catenin expression in osteosarcoma patients was associated with clinical prognosis. Conclusively, the present study provides comprehensive evidence for the inhibition of dioscin on osteosarcoma stem-cell-like properties and tumor growth through repression of Akt/GSK3/β-catenin pathway, which suggests dioscin as a promising therapeutic regimen. And β-catenin may be a potential therapeutic target as well as a significant prognostic marker for osteosarcoma patients in clinic.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Milk Thistle Seed Extract Silymarin, Silibin, Silibinin

Eur J Pharmacol

actions:

. 2018 Aug 5;832:39-49. doi: 10.1016/j.ejphar.2018.05.027. Epub 2018 May 19.

Combined treatment with sorafenib and silibinin synergistically targets both HCC cells and

cancer stem cells by enhanced inhibition of the phosphorylation of STAT3/ERK/AKT

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• PMID: 29782854 DOI: 10.1016/j.ejphar.2018.05.027

Abstract

Silibinin, a nontoxic bioactive component in milk thistle, is used as a liver-protective drug in the clinic mainly because of its antioxidant and anti-inflammation activities. In this study, we studied the cytotoxic effects of silibinin combined with sorafenib on hepatocellular carcinoma (HCC). The results indicated that silibinin combined with sorafenib potently inhibited the proliferation of various HCC cells and induced significant apoptosis. In an HCC subcutaneous transplantation tumor model, **the combination of silibinin and sorafenib significantly suppressed tumor growth compared with monotherapy. As determined by fluorescence staining and Western blots, the combination of the two drugs inhibited the phosphorylation of RAC-alpha serine/threonine-protein kinase (AKT) and signal transducer and activator of transcription 3 (STAT3) together with the expression of antiapoptotic proteins including myeloid leukemia cell differentiation protein Mcl-1 (Mcl-1) and apoptosis regulator Bcl-2 (Bcl-2), resulting in the death of cancer cells. We also found that the combination inhibited the formation and self-renewal of HCC stem cells by down-regulating the expression of stemness-related proteins, such as Homeobox protein NANOG (Nanog) and Krueppel-like factor 4 (Klf4). These results suggested that silibinin improved the efficacy of sorafenib in HCC therapy, indicating a clinical promising therapeutic strategy for HCC patients.**

Keywords: Cancer stem cell; Drug combination; Hepatocellular carcinoma; Silibinin; Sorafenib.

Sci Rep
actions:
. 2018 Nov 19;8(1):16985. doi: 10.1038/s41598-018-35069-0.

Silibinin, A Natural Blend In Polytherapy Formulation For Targeting Cd44v6 Expressing Colon Cancer Stem Cells

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- PMID: 30451890 PMCID: PMC6242811 DOI: 10.1038/s41598-018-35069-0

Free PMC article

Full-text links Cite

Erratum in

- Publisher Correction: Silibinin, A Natural Blend In Polytherapy Formulation For Targeting Cd44v6 Expressing Colon Cancer Stem Cells. Patel S, Waghela B, Shah K, Vaidya F, Mirza S, Patel S, Pathak C, Rawal R.
  Sci Rep. 2018 Dec 17;8(1):17992. doi: 10.1038/s41598-018-36920-0. PMID: 30559397 **Free PMC article.**

Abstract

Colon cancer stem cells have been attributed to poor prognosis, therapeutic resistance and aggressive nature of the malignancy. Recent reports associated CD44v6 expression with relapse, metastasis and reduced 5-year survival of colon cancer patients, thereby making it a potential therapeutic target. Thus, in this study, comprehensive prediction and screening of CD44v6 against 1674 lead compounds was conducted. **Silibinin was identified as a potential compound targeting CD44v6.** Inorder to substantiate these findings, the cytotoxic effect of 5FU, Silibinin and 5FU+ Silibinin was assessed on human colon carcinoma cell line HCT116 derived CD44+ subpopulation. 5FU+ Silibinin inhibited cell proliferation of CD44+ subpopulation at lower concentration than Silibinin standalone. Further, corresponding to CD44v6 knockdown cells, 5FU+ Silibinin treatment significantly decreased CD44v6, Nanog, CTNNB1 and CDKN2A expression whereas increased E-cadherin expression in HCT116

derived CD44+ cells. **Moreover, synergistic effect of these drugs suppressed sphere formation, inhibited cell migration, triggered PARP cleavage and perturbation in mitochondrial membrane potential, thereby activating intrinsic apoptotic pathways and induced autophagic cell death. Importantly, 5FU+ Silibinin could inhibit PI3K/MAPK dual activation and arrest the cell cycle at G0/G1 phase. Thus, our study suggests that inhibition of CD44v6 attenuates stemness of colon cancer stem cells and holds a prospect of potent therapeutic target.**

Brain Res
actions:
. 2015 Dec 10;1629:85-93. doi: 10.1016/j.brainres.2015.10.010. Epub 2015 Oct 22.

Synergistic anti-tumor actions of luteolin and silibinin prevented cell migration and invasion and induced apoptosis in glioblastoma SNB19 cells and glioblastoma stem cells

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- PMID: 26471408 DOI: 10.1016/j.brainres.2015.10.010

Full-text links Cite

Abstract

Glioblastoma is the most lethal brain tumor. Failure of conventional chemotherapies prompted the search for natural compounds for treatment of glioblastoma. Plant-derived flavonoids could be

alternative medicine for inhibiting not only glioblastoma cells but also glioblastoma stem cells (GSC). Two plant-derived flavonoids are luteolin (LUT) and silibinin (SIL). We investigated anti-tumor mechanisms of LUT and SIL in different human glioblastoma cells and GSC and found significant synergistic inhibition of human glioblastoma LN18 and SNB19 cells and GSC following treatment with combination of 20μM LUT and 50μM SIL. Combination of 20μM LUT and 50μM SIL was more effective than a conventional chemotherapeutic agent (BCNU or TMZ). We continued our studies with SNB19 cells and GSC and found dramatic inhibition of cell migration from spheroids and also cell invasion through matrigel following treatment with combination of LUT and SIL. **This combination was highly effective to block angiogenesis and survival pathways leading to induction of apoptosis. Inhibition of PKCα, XIAP, and iNOS ultimately caused induction of extrinsic and intrinsic pathways of apoptosis. Collectively, synergistic efficacy of LUT and SIL could be a promising therapy to inhibit cell migration and invasion and induce apoptosis in different glioblastoma cells including GSC.**

Keywords: Apoptosis; Cell migration; Glioblastoma stem cells; Luteolin; SNB19; Silibinin.

Eur J Cancer
actions:
. 1996 May;32A(5):877-82. doi: 10.1016/0959-8049(96)00011-1.

Antiproliferative effect of silybin on gynaecological malignancies: synergism with cisplatin and doxorubicin

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• PMID: 9081370 DOI: 10.1016/0959-8049(96)00011-1

Abstract

The aim of this study was to test the antiproliferative activity of silybin, a flavonoid, on human ovarian and breast cancer cell lines. Since flavonoids are thought to act through Type II oestrogen binding sites (Type II EBS), silybin binding to Type II EBS was also examined. Silybin, used in concentrations from 0.1 to 20 microM, exerted a dose-dependent growth inhibitory effect on OVCA 433, A2780 parental and drug-resistant ovarian cancer cells, and MCF-7 doxorubicin (DOX)-resistant breast cancer cells (IC50 = 4.8-24 microM). Both L and D diastereoisomers of silybin were effective in inhibiting A2780 WT cell growth (IC50 = 14 and 20 microM, respectively). Flow cytometry revealed that silybin decreased the percentage of cells in the S and G2-M phases of the cell cycle with a concomitant increase in cells in the G0-G1 phase. Silybin was able to compete with [3H]E2 for nuclear but not cytosolic Type II EBS. Its affinity parallels its efficacy in inhibiting cell proliferation. Furthermore, silybin (0.1 and 1 microM) potentiates the effect of cisplatin (CDDP) (0.1-1 micrograms/ml) in inhibiting A2780 WT and CDDP-resistant cell growth. Similar results were obtained on MCF-7 DOX-resistant cells when silybin (0.1 microM) was associated with doxorubicin (0.1-10 micrograms/ml). As assessed by the Berembaum isobole method, **the effect of silybin-CDDP and silybin-DOX combinations results in a synergistic action. Using the 'stem cell assay' described by Hamburger and Salmon [Science 1977, 197, 461-463], we found that silybin exerted a dose-dependent inhibition of clonogenic efficiency of cells derived from three ovarian tumours (IC50 = 7.4, 4 and 6.4 microM, respectively). Since CDDP and DOX are the two most commonly used drugs for gynaecological tumours, the clinical application of silybin is currently under investigation in our institute.**

Review
Anticancer Res
actions:
. 2015 Nov;35(11):5773-88.

Natural Products That Target Cancer Stem Cells

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- PMID: 26503998

Abstract

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

Keywords: Dietary agents; cancer stem cells; mechanism of action; review; signal transduction pathways.

Review Article

Nutrients
. 2020 Mar 13;12(3):761. doi: 10.3390/nu12030761.

Flavonoids and Other Polyphenols Act as Epigenetic Modifiers in Breast Cancer

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• PMID: 32183060 PMCID: PMC7146477 DOI: 10.3390/ nu12030761
Free PMC article

Abstract
Breast cancer is a common cancer that occurs due to different epigenetic alterations and genetic mutations. Various epidemiological studies have demonstrated an inverse correlation between breast cancer incidence and flavonoid intake. The anti-cancer action of flavonoids, a class of polyphenolic compounds that are present in plants, as secondary metabolites has been a major topic of research for many years. Our review analysis demonstrates that flavonoids exhibit anticancer activity against breast cancer occurring in different ethnic populations. Breast cancer subtype and menopausal status are the key factors in inducing the flavonoid's anti-cancer action in breast cancer. The dose is another key factor, with research showing that approximately 10 mg/day of isoflavones is required to inhibit breast cancer occurrence. In addition, flavonoids also influence the epigenetic machinery in breast cancer, with research demonstrating that epigallocatechin, genistein, and resveratrol all inhibited DNA methyltransferase and altered chromatin modification in breast cancer. These flavonoids can induce the expression of different tumor suppressor genes that may contribute to decreasing breast cancer progression and metastasis. Additional studies are required to confirm the contribution of epigenetic modifications by flavonoids to breast cancer prevention.

Keywords: Epigenetics; breast cancer; chromatin modification; flavonoids; methylation.

Am J Clin Nutr
actions
. 2000 Dec;72(6):1424-35. doi: 10.1093/ajcn/72.6.1424.

Bitter taste, phytonutrients, and the consumer: a review

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• PMID: 11101467 DOI: 10.1093/ajcn/72.6.1424

Abstract

Dietary phytonutrients found in vegetables and fruit appear to lower the risk of cancer and cardiovascular disease. Studies on the mechanisms of chemoprotection have focused on the biological activity of plant-based phenols and polyphenols, flavonoids, isoflavones, terpenes, and glucosinolates. Enhancing the phytonutrient content of plant foods through selective breeding or genetic improvement is a potent dietary option for disease prevention. However, most, if not all, of these bioactive compounds are bitter, acrid, or astringent and therefore aversive to the consumer. Some have long been viewed as plant-based toxins. As a result, the food industry routinely removes these compounds from plant foods through selective breeding and a variety of debittering processes. This poses a dilemma for the designers of functional foods because increasing the content of bitter phytonutrients for health may be wholly incompatible with consumer acceptance. Studies on phytonutrients and health ought to take sensory factors and food preferences into account.