Cancer Stem Cells & How to Eradicate

1

Carcinogenesis (CSCs)

- The two dominant models of carcinogenesis postulate stochastic (clonal evolution) or hierarchic organization of tumor (cancer stem cell model).
- According to the latter, at the germinal center of tumor evolution is a **cancer stem cell (CSC)** which, **similar to normal adult stem cells, possesses the capacity of self-renewal and a differentiation potential**.
- Over the past few years, compelling evidence has emerged in support of the hierarchic cancer model for many solid tumors including hepatocellular cancers.
- **The CSCs are posited to be responsible not only for tumor initiation but also for the generation of distant metastasis and relapse after therapy**.
- These characteristics are particularly relevant for a multi-resistant tumor entity like human hepatocellular carcinoma and may herald a paradigm shift in the management of this deadly disease.
- J Hepatol. 2010 Sep;53(3):568-77. doi: 10.1016/j.jhep.2010.05.003. Epub 2010 May 31. PMID: 20646772; PMCID: PMC3492877.

2

Cancer Stem Cells (CSCs)

- Cancer stem cells (CSCs) have been suggested to be responsible for tumor re-growth and relapse.
- They do not contain hormone receptors.
- Physiological and morphological knowledge of CSCs may be essential for the development of new therapeutic strategies targeting cancer development, progression, and recurrence.
- Energy metabolism and mitochondrial function are important factors operating on stemness maintenance and cell fate specification. Due to the role of mitochondria as central hubs in the overall cell metabolism and death and survival pathways, research on their physiology in CSCs is of paramount importance to decipher mechanisms underlying their therapy-resistant phenotype.
- Mitochondrial biology in cancer stem cells. Semin Cancer Biol. 2017 Dec;47:18-28. doi: 10.1016/j.semcancer.2017.06.012. Epub 2017 Jun 30. PMID: 28673608.

3

CSCs

- Cancer stem cells (CSCs) are subpopulations of tumor masses with unique abilities in self-renewal, stemness maintenance, drug resistance, and the promotion of cancer recurrence.
- Recent studies have suggested that breast CSCs play essential roles in chemoresistance.
- Luteolin Inhibits Breast Cancer Stemness and Enhances Chemosensitivity through the Nrf2-Mediated Pathway. Molecules. 2021 Oct 26;26(21):6452. doi: 10.3390/molecules26216452. PMID: 34770867; PMCID: PMC8587415.

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Undifferentiaed > Cancer Stem Cells > Drive Primary & Recurrences

- Although we have come a long way in our understanding of the signals that drive cancer growth, and how these signals can be targeted, effective control of this disease remains a key scientific and medical challenge.
- The therapy resistance and relapse that are commonly seen are driven in large part by the inherent heterogeneity within cancers that allows drugs to effectively eliminate some, but not all, malignant cells.
- Here, we focus on the fundamental drivers of this heterogeneity by examining emerging evidence that shows that these traits are often controlled by the **disruption of normal cell fate and aberrant adoption of stem cell signals**.
- We discuss how undifferentiated cells are preferentially primed for transformation and often serve as the cell of origin for cancers.
- We also consider evidence showing that activation of **stem cell** programmes in cancers can lead to progression, therapy resistance and metastatic growth and that targeting these attributes may enable better control over a difficult disease.
- Stem cell fate in cancer growth, progression and therapy resistance. Nat Rev Cancer. 2018 Nov;18(11):669-680. doi: 10.1038/s41568-018-0056-x. PMID: 30228301; PMCID: PMC8388042.

5

CSCs- not effected by radiation or chemo

- Recent data suggesting many cancers arise from rare self-renewing cells (cancer stem cells) that are biologically distinct from their more numerous differentiated progeny may explain this paradox.
- Current anticancer therapies have been developed to target the bulk of the tumor mass (ie, the differentiated cancer cells).
- Although treatments directed against the bulk of the cancer may produce dramatic responses, they are unlikely to result in long-term remissions if the rare cancer stem cells are also not targeted.
- Better understanding the biology of cancer stem cells and re-examining our preclinical and clinical drug development paradigms to include the cancer stem cell concept have the potential to revolutionize the treatment of many cancers.
- Cancer Stem Cells: From Bench to Bedside Biology of Blood and Marrow Transplantation Volume 13, Supplement 1, January 2007, Pages 47-52

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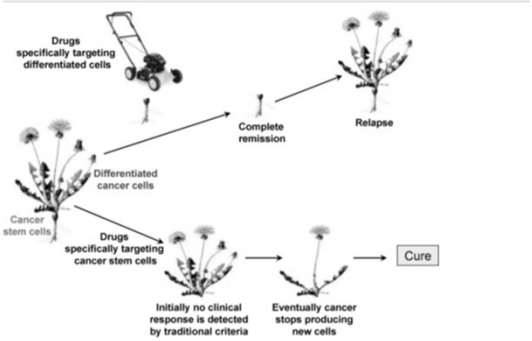
Thus, improving the results of cancer therapy requires identification and better understanding the biology of cancer stem cells, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Cancer Stem Cells: From Bench to Bedside. Biol Blood Marrow Transplant. 2007 Jan;13(Suppl 1):47-52.



7

Cancer Stem Cells – Vulnerable to Local Environment

- **Cancer stem cells (CSCs) are a subset of cancer cells with a stem cell-like ability, which may drive tumor growth and recurrence and are resistant to many current anticancer treatments**.
- Solid tumors are regarded as "organs" which are comprised of cancer cells and the tumor stroma.
- The tumor microenvironment makes up the stroma of the tumor, which occupies the majority of the tumor mass, including the extracellular matrix (ECM), mesenchymal stem cells (MSCs), endothelial cells, immune cells, and, what is more, networks of cytokines and growth factors.
- **The microenvironment or niche surrounding CSCs largely governs their cellular fate**.
- The cancer stem cell niche: cross talk between cancer stem cells and their microenvironment. Tumour Biol. 2014 May;35(5):3945-51. doi: 10.1007/s13277-013-1561-x. Epub 2014 Jan 14. PMID: 24420150.

8

What fights CSCs?

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Iodine - Molecular iodine inhibits the expression of stemness markers on cancer stem-like cells of established cell lines derived from cervical cancer

- **Background:** Cancer stem cells (CSC) are characterized by deregulated self-renewal, tumorigenicity, metastatic potential, aberrant stemness signaling pathways, resistance to conventional therapy, and the ability to give rise to a progeny of proliferating cells that constitute the bulk of tumors.
- Targeting CSC will provide novel treatments for cancer.
- . Since, it has been reported that molecular iodine (I_2) exhibits antineoplastic effects and decreases tumor progression in some cancer models, we evaluated the potential effect of I_2 on cell cultures enriched in cervical cancer stem-like cells.
- **Methods:** HeLa and SiHa cervical cancer cells were treated with 200uM I_2 for 24 h. After time, cells were cultured in CSC-conditioned medium (cervospheres) and viability assays were performed. Following, tumorigenic capabilities in cervospheres treated with I_2 were evaluated in NOD/SCID mice. HeLa monolayer cells untreated and their respective cervosphere cells treated or untreated with 200 μM of I_2 for 24 h were xenotransplanted subcutaneously at different amounts and mice were monitored for at least 2 months.
- **Results:** In the present study, monolayer and CSC-enriched cultures (cervospheres) from cervical cancer-derived cell lines, HeLa and SiHa, showed that 200uM I_2 supplementation inhibits proliferation of both and decreased their tumorigenic capacity, in vivo.
- **This antineoplastic effect of I_2** was accompanied by diminished expression of stemness markers including CD49f, CK17, OCT-4, NANOG, SOX2, and KLF4, as well as increased expression and activation of PPARγ receptors.
- **Conclusions:** All this data led us to suggest a clinical potential use of I_2 for targeting CSC and improve current treatments against cervical cancer.
- iodine inhibits the expression of stemness markers on cancer stem-like cells of established cell lines derived from cervical cancer. BMC Cancer. 2018 Sep 26;18(1):928. doi: 10.1186/s12885-018-4824-5. PMID: 30257666; PMCID: PMC6158890.

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Iodine

- **Molecular iodine has been studied in several cancer cell lines showing its ability to inhibit proliferation, chemo-resistance, and apoptotic effects.**

- Antiproliferative/cytotoxic activity of molecular iodine and iodolactones in various human carcinoma cell lines. No interfering with EGF-signaling, but evidence for apoptosis. *Exp Clin Endocrinol Diabetes.* 2009;**118**(7):410–419. doi: 10.1055/s-0029-1225615.
- . Iodide excess induces apoptosis in thyroid cells through a p53-independent mechanism involving oxidative stress. *Endocrinology.* 2000;**141**(2):598–605. doi: 10.1210/endo.141.2.7291.
- Signaling pathways involved in the antiproliferative effect of molecular iodine in normal and tumoral breast cells: evidence that 6-iodolactone mediates apoptotic effects. *Endocr Relat Cancer.* 2008;**15**(4):1003–1011. doi: 10.1677/ERC-08-0125.
- A complex between 6-iodolactone and the peroxisome proliferator-activated receptor type gamma may mediate the antineoplastic effect of iodine in mammary cancer. *Prostaglandins Other Lipid Mediat.* 2009;**89**(1–2):34–42. doi: 10.1016/j.prostaglandins.2009.04.001.
- 6-iodolactone, key mediator of antitumoral properties of iodine. *Prostaglandins Other Lipid Mediat.* 2014;**112**:27–33. doi: 10.1016/j.prostaglandins.2014.07.001.
- . Molecular iodine impairs chemoresistance mechanisms, enhances doxorubicin retention and induces downregulation of the CD44+/CD24+ and E-cadherin+/vimentin+ subpopulations in MCF-7 cells resistant to low doses of doxorubicin. *Oncol Rep.* 2017;**38**(5):2867–2876. doi: 10.3892/or.2017.5934. [

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Iodine decreases CSCs

- Conclusions
- In resume, our results demonstrate the I_2-mediated cytotoxic effect in CSC derived from cervical cancer cell lines, in which CD49f, CK17 and stemness marker positive cells are decreased.
- Since I_2 supplements are considered to be safe for the treatment of diseases such as human mammary fibrocystic disease, breast cancer or prostate hyperplasia (reviewed in [30]), we suggest that I_2 treatment for cancer should be studied in preclinical trials to evaluate its potential anti-cancer effect alone or in a combination with conventional therapeutic drugs, to eliminate cancer stem cells from cervical cancer and others.
- Molecular iodine inhibits the expression of stemness markers on cancer stem-like cells of established cell lines derived from cervical cancer. BMC Cancer. 2018 Sep 26;18(1):928. doi: 10.1186/s12885-018-4824-5. PMID: 30257666; PMCID: PMC6158890.
- Antiproliferative/cytotoxic activity of molecular iodine and iodolactones in various human carcinoma cell lines. No interfering with EGF-signaling, but evidence for apoptosis. *Exp Clin Endocrinol Diabetes.* 2009;**118**(7):410–419. doi: 10.1055/s-0029-1225615

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Iodine – antiprolierative in the breast against ER+ BC cells not damaging to normal parenchyma

- Twelve human cancer cell lines and one non-malignant cell line were investigated with respect to a potential antiproliferative/cytotoxic activity of molecular iodine and iodolactones.
- **Except CCL221 colon carcinoma cells, the growth of all cancer cell lines decreased if the cells were cultured in the presence of 10 microM molecular iodine (I(2)) for at least two days**.
- Delta-iodolactone (IL, 5 microM) was found to have a similar effect.
- SH-SY5Y neuroblastoma cells turned out to be most susceptible to both iodine compounds (total inhibition), followed by **MCF-7 mammary carcinoma cells (60% and 77.7% inhibition in the presence of I(2) respect**. IL) and HS24 lung carcinoma cells (36.3% respect. 40.3% inhibition).
- In contrast, MCF-10 normal mammary epithelial cells were much less affected by the iodine treatment.
- A disruption by molecular iodine of mitochondrial transmembrane electrical potential, which was prevented by a pre-treatment of the cells with N-acetyl-cysteine, supports a mitochondria-mediated apoptotic mechanism.
- Antiproliferative/cytotoxic activity of molecular iodine and iodolactones in various human carcinoma cell lines. No interfering with EGF-signaling, but evidence for apoptosis. Exp Clin Endocrinol Diabetes. 2010 Jul;118(7):410-9. doi: 10.1055/s-0029-1225615. Epub 2009 Oct 2. PMID: 19802778.

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Iodine - Breast & Thyroid Cancer

- **Objective:** As we previously demonstrated, the inhibitory effect of iodine on thyroid cell growth is mediated by iodolactones, especially 6-iodo-5-hydroxy-eicosatrienoic acid (delta-iodolactone). In this communication we compare the effect of iodide, molecular iodine and delta-iodolactone on growth inhibition and apoptosis on three human thyroid carcinoma cell lines (B-CPAP cells, FTC-133 cells and 8505C cells) as well as on human breast cancer cells (MCF 7
- **Conclusion:** delta-Iotaodolactone seems to be the main iodocompound which can inhibit growth and induce apoptosis in B-CPAP cells as well as in MCF 7 breast cancer cells.
- The role of iodine and delta-iodolactone in growth and apoptosis of malignant thyroid epithelial cells and breast cancer cells. Hormones (Athens). 2010 Jan-Mar;9(1):60-6. doi: 10.14310/horm.2002.1254. PMID: 20363723.

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Iodine

- Most investigations of iodine metabolism in humans and animals have focused on its role in thyroid function. However, considerable evidence indicates that iodine could also be implicated in the physiopathology of other organs.
- We review the literature that shows that molecular iodine (I_2) exerts multiple and complex actions on the organs that capture it, not including its effects as part of thyroid hormones. This chemical form of iodine is internalized by a facilitated diffusion system that is evolutionary conserved, and its effects appear to be mediated by a variety of mechanisms and pathways.
- As an oxidized component, it directly neutralizes free radicals, induces the expression of type II antioxidant enzymes, or inactivates proinflammatory pathways.
- In neoplastic cells, I_2 generates iodolipids with nuclear actions that include the activation of apoptotic pathways and the inhibition of markers related to stem cell maintenance, chemoresistance, and survival.
- Recently, I2 has been postulated as an immune modulator that depending on the cellular context, can function as an inhibitor or activator of immune responses.
- We propose that the intake of molecular iodine is increased in adults to at least 1 mg/day in specific pathologies to obtain the potential extrathyroid benefits described in this review.

- Molecular Iodine Has Extrathyroidal Effects as an Antioxidant, Differentiator, and Immunomodulator. Int J Mol Sci. 2021 Jan 27;22(3):1228. doi: 10.3390/ijms22031228. PMID: 33513754; PMCID: PMC7865438.

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Iodine – Triple Negative BC

- **Background:** The immune system is a crucial component in cancer progression or regression. Molecular iodine (I_2) exerts significant antineoplastic effects, acting as a differentiation inductor and immune modulator, but its effects in antitumor immune response are not elucidated.
- **Methods:** The present work analyzed the effect of I_2 in human breast cancer cell lines with low (MCF-7) and high (MDA-MB231) metastatic potential under both in vitro (cell proliferation and invasion assay) and in vivo (xenografts of athymic nude mice) conditions.
- **Conclusions:** I_2 decreases the invasive potential of a triple negative basal cancer cell line, and under in vivo conditions the oral supplement of this halogen activates the antitumor immune response, preventing progression of xenografts from laminal and basal mammary cancer cells. These effects allow us to propose iodine supplementation as a possible adjuvant in breast cancer therapy.
- Molecular iodine exerts antineoplastic effects by diminishing proliferation and invasive potential and activating the immune response in mammary cancer xenografts. BMC Cancer. 2019 Mar 22;19(1):261. doi: 10.1186/s12885-019-5437-3. PMID: 30902074; PMCID: PMC6431076.

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X Iodine – Hashimoto's

- Hashimoto's thyroiditis (HT) is a chronic autoimmune thyroid disease caused by an interaction between genetic factors and environmental conditions, both of which are yet to be fully understood. The management of HT depends on its clinical manifestations, commonly including diffuse or nodular goiter with euthyroidism, subclinical hypothyroidism and permanent hypothyroidism. However, in most cases of patients with HT, lifelong levothyroxine substitution is required.
- The additional role of diet for the management of HT is usually overlooked.
- A literature search regarding the importance and the influence of iodine, selenium, vitamin D and gluten on HT was conducted. In HT careful supplementation of possible deficiencies is recommended for the dietary management of these patients.
- The use of a diet low in gluten among HT patients with or without celiac disease (CD) is discussed.

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Apigenin

- Apigenin inhibits the self-renewal capacity of human ovarian cancer SKOV3-derived sphere-forming cells. Mol Med Rep. 2015 Mar;11(3):2221-6. doi: 10.3892/mmr.2014.2974. Epub 2014 Nov 18. PMID: 25405327.

18

Soy

- Accumulating evidence has demonstrated that cancer stem cells (CSCs) play an essential role in tumor progression and reoccurrence and drug resistance.
- Emerging evidence indicates that numerous chemopreventive compounds, also known as nutraceuticals, could eliminate CSCs in part via regulating several signaling pathways.
- Therefore, in this review, we will describe the some natural chemopreventive agents that target CSCs in a variety of human malignancies, including soy isoflavone, curcumin, resveratrol, tea polyphenols, sulforaphane, quercetin, indole-3-carbinol, 3,3'-diindolylmethane, withaferin A, apigenin, etc.
- Moreover, we discuss that eliminating CSCs by nutraceuticals might be a promising strategy for treating human cancer via overcoming drug resistance and reducing tumor reoccurrence.
- Targeting cancer stem cells by nutraceuticals for cancer therapy. Semin Cancer Biol. 2022 Oct;85:234-245. doi: 10.1016/j.semcancer.2021.07.008. Epub 2021 Jul 14. PMID: 34273521.

19

Soy

- To Soy Or Not To Soy

- Safe Hormones, Smart Women Berkson DL Awakened Medicine Press

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Soy

- Soy isoflavones are dietary components for which an association has been demonstrated with reduced risk of prostate cancer (PCa) in Asian populations. However, the exact mechanism by which these isoflavones may prevent the development or progression of PCa is not completely understood.
- The predominant and most biologically active isoflavones in soy products, genistein, daidzein, equol, and glycetin, inhibit prostate carcinogenesis in some animal models. Cell-based studies show that soy isoflavones regulate genes that control cell cycle and apoptosis.
- In this review, we discuss the literature relevant to the molecular events that may account for the benefit of soy isoflavones in PCa prevention or treatment.
- These reports show that although soy isoflavone-induced growth arrest and apoptosis of PCa cells are plausible mechanisms, other chemo protective mechanisms are also worthy of consideration. These possible mechanisms include antioxidant defense, DNA repair, inhibition of angiogenesis and metastasis, potentiation of radio- and chemotherapeutic agents, and antagonism of estrogen- and androgen-mediated signaling pathways.
- Moreover, other cells in the cancer milieu, such as the fibroblastic stromal cells, endothelial cells, and immune cells, may be targeted by soy isoflavones, which may contribute to soy-mediated prostate cancer prevention.
- Soy isoflavones and prostate cancer: a review of molecular mechanisms. J Steroid Biochem Mol Biol. 2014 Mar;140:116-32. doi: 10.1016/j.jsbmb.2013.12.010. Epub 2013 Dec 25. PMID: 24373791; PMCID: PMC3962012.

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Apigenin

- The aim of this study is to present a critical and broad evaluation of the anti-CSC capability of apigenin and isovitexin in different cancers as novel and untapped natural compounds for developing drugs. A thorough review of the included literature supports a strong association between anti-CSC activity and treatment with apigenin or isovitexin. Additionally, it has been shown that apigenin or isovitexin affected CSC metabolism and reduced CSCs through various mechanisms, including the suppression of the Wnt/β-catenin signaling pathway, the inhibition of nuclear factor-κB protein expression, and the downregulation of the cell cycle via upregulation of p21 and cyclin-dependent kinases. The findings of this study demonstrate that apigenin and isovitexin are potent candidates for treating cancer due to their antagonistic effects on CSC metabolism.
- Anticancer Potential of Apigenin and Isovitexin with Focus on Oncogenic Metabolism in Cancer Stem Cells. Metabolites. 2023 Mar 9;13(3):404. doi: 10.3390/metabo13030404. PMID: 36984844; PMCID: PMC10051376.

22

Sulphorophane

- Cancer stem cells (CSCs) constitute a subpopulation of tumor cells that possess self-renewal and tumor initiation capacity, and the ability to give rise to the heterogeneous lineages of cancer cells that comprise the tumor.
- CSCs exhibit intrinsic mechanisms of resistance to virtually all conventional cancer therapeutics, allowing them to survive current cancer therapies and to initiate tumor recurrence and metastasis.
- Different pathways and mechanisms that confer resistance and survival of CSCs, including activation of the Wnt/β- catenin, Sonic Hedgehog, Notch, PI3K/Akt/mTOR and STAT3 signaling pathways, expression of aldehyde dehydrogenase 1 (ALDH1) and oncogenic microRNAs, and acquisition of epithelial-mesenchymal transition (EMT), have been identified recently.
- Certain phytochemicals, in particular curcumin, epigallocatechin-3-gallate (EGCG), sulforaphane, resveratrol and genistein have been shown to interfere with these intrinsic CSC pathways in vitro and in human xenograft mice, leading to elimination of CSCs.
- Moreover, recent clinical trials have demonstrated the therapeutic efficacy of five phytochemicals, alone or in combination with modern cancer therapeutics, and in various types of cancer.
- **Since current cancer therapies fail to eradicate CSCs,** leading to cancer recurrence and progression, targeting of CSCs with phytochemicals such as curcumin, EGCG, sulforaphane, resveratrol and genistein, combined with each other and/or in combination with conventional cytotoxic drugs and novel cancer therapeutics, may offer a novel therapeutic strategy against cancer.
- Phytochemicals Targeting Cancer Stem Cells: Curcumin, EGCG, Sulforaphane, Resveratrol and Genistein. Curr Med Chem. 2021;28(22):4321-4342. doi: 10.2174/0929867327666200228110738. PMID: 32107991.

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Plant flavone apigenin: An emerging anticancer agent

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X Apigenin

- Compounds known as flavonoids categorized anthocyanidins, flavonols, flavanones, flavonols, flavones, and isoflavones have shown considerable promise as chemopreventive agents.
- Apigenin (4', 5, 7-trihydroxyflavone), a major plant flavone, possessing antioxidant, anti-inflammatory, and anticancer properties affecting several molecular and cellular targets used to treat various human diseases.
- Epidemiologic and case-control studies have suggested apigenin reduces the risk of certain cancers.
- Studies demonstrate that apigenin retain potent therapeutic properties alone and/or increases the efficacy of several chemotherapeutic drugs in combination on a variety of human cancers.
- Apigenin's anticancer effects could also be due to its differential effects in causing minimal toxicity to normal cells with delayed plasma clearance and slow decomposition in liver increasing the systemic bioavailability in pharmacokinetic studies.
- Here we discuss the anticancer role of apigenin highlighting its potential activity as a chemopreventive and therapeutic agent.
- Plant flavone apigenin: An emerging anticancer agent. Curr Pharmacol Rep. 2017 Dec;3(6):423-446. doi: 10.1007/s40495-017-0113-2. Epub 2017 Oct 14. PMID: 29399439; PMCID: PMC5791748.

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Dried parsley is highest source

- Apigenin is found as a single ingredient in chamomile tea, obtained from the dried flowers of *Matricaria chamomilla*, an annual herb native to Western Asia and Europe; naturalized in Australia, Britain, and the United States. Drinks prepared from chamomile contains 0.8% to 1.2% apigenin and essential oils possessing aromatic, flavoring, and coloring properties.
- Apigenin is also a component of red wine and beer.
- Dried parsley has been reported to have the maximum quantity of apigenin, at 45,035 µg/g.
- Additional sources of apigenin are dried flower of chamomile, containing 3,000 to 5,000 µg/g; celery seeds, containing 786.5 µg/g; and vine spinach and Chinese celery, containing 622 µg/g and 240.2 µg/g.
- Role of Apigenin in Cancer Prevention via the Induction of Apoptosis and Autophagy. *J Cancer Prev.* 2016;21:216–226

26

Parsley induces Grand Dame Of Tumor Suppression "P53"

- Several studies have demonstrated that the anticarcinogenic properties of apigenin occur through regulation of cellular response to oxidative stress and DNA damage, suppression of inflammation and angiogenesis, retardation of cell proliferation, and induction of autophagy and apoptosis.
- **One of the most well-recognized mechanisms of apigenin is the capability to promote cell cycle arrest and induction of apoptosis through the p53-related pathway**.
- **A further role of apigenin in chemoprevention is the induction of autophagy** in several human cancer cell lines. In this review, we discuss the details of apigenin, apoptosis, autophagy, and the role of apigenin in cancer chemoprevention via the induction of apoptosis and autophagy.
- Role of Apigenin in Cancer Prevention via the Induction of Apoptosis and Autophagy. J Cancer Prev. 2016 Dec;21(4):216-226. doi: 10.15430/JCP.2016.21.4.216. Epub 2016 Dec 30. PMID: 28053955; PMCID: PMC5207605.

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Apigenin

- Cancer stem cells (CSCs) of endocrine tumors have received more attention due to their role in cancer progression, therapeutic resistance, and cancer relapse. Phytochemicals provide several health benefits and are effective in the treatment of various diseases including cancer. Therefore, finding the natural phytochemicals that target the CSCs will help to improve cancer patients' prognosis and life expectancy. Phytochemicals have been shown to have anticancer properties and are very effective in treating various cancer types.
- Other phytochemicals such as apigenin are effective against different endocrine cancers by regulating the CSCs.
- Targeting the Cancer Stem Cells in Endocrine Cancers with Phytochemicals. Curr Top Med Chem. 2022;22(31):2589-2597. doi: 10.2174/1567205020666221114112814. PMID: 36380414.

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Apigenin – Anticancer Agent

- Apigenin is an edible plant-derived flavonoid that has been reported as an anticancer agent in several experimental and biological studies. It exhibits cell growth arrest and apoptosis in different types of tumors such as breast, lung, liver, skin, blood, colon, prostate, pancreatic, cervical, oral, and stomach, by modulating several signaling pathways.
- Apigenin induces apoptosis by the activation of extrinsic caspase-dependent pathway by upregulating the mRNA expressions of caspase-3, caspase-8, and TNF-α.
- It induces intrinsic apoptosis pathway as evidenced by the induction of cytochrome c, Bax, and caspase-3, while caspase-8, TNF-α, and B-cell lymphoma 2 levels remained unchanged in human prostate cancer PC-3 cells.
- Apigenin treatment leads to significant downregulation of matrix metallopeptidases-2, -9, Snail, and Slug, suppressing invasion. The expressions of NF-κB p105/p50, PI3K, Akt, and the phosphorylation of p-Akt decreases after treatment with apigenin. However, apigenin-mediated treatment significantly reduces pluripotency marker Oct3/4 protein expression which might be associated with the downregulation of PI3K/Akt/NF-κB signaling.
- Apigenin as an anticancer agent. Phytother Res. 2020 Aug;34(8):1812-1828. doi: 10.1002/ptr.6647. Epub 2020 Feb 14. PMID: 32059077.

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Apigenin – chemo sensitizing agent

- Analysis of the data from the studied cancer models has revealed that apigenin exerts its anti-proliferative effects through multiple and complex pathways.
- This guided us to discover some controversial results about the exact role of certain molecular pathways such as autophagy in the anticancer effects of apigenin.
- Further, there were cumulative positive evidences supporting the involvement of certain pathways such as apoptosis, ROS and DNA damage and repair.
- Apigenin possesses a high potential to be used as a chemosensitizing agent through the up-regulation of DR5 pathway.
- Apigenin: A dietary flavonoid with diverse anticancer properties. Cancer Lett. 2018 Jan 28;413:11-22. doi: 10.1016/j.canlet.2017.10.041. Epub 2017 Oct 31. PMID: 29097249.
- Apigenin's anticancer properties and molecular mechanisms of action: Recent advances and future prospectives. Chin J Nat Med. 2017 May;15(5):321-329. doi: 10.1016/S1875-5364(17)30052-3. PMID: 28558867.

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Apigenin

- Malignant melanoma is the most invasive and fatal form of cutaneous cancer. Moreover it is extremely resistant to conventional chemotherapy and radiotherapy.
- **Apigenin, a non-mutagenic flavonoid, has been found to exhibit chemopreventive and/or anticancerogenic properties in many different types of human cancer cells**.
- In the present study, we investigated the effects of apigenin on the viability, migration and invasion potential, dendrite morphology, cell cycle distribution, apoptosis, phosphorylation of the extracellular signal-regulated protein kinase (ERK) and the AKT/mTOR signaling pathway in human melanoma A375 and C8161 cell lines in vitro.
- Apigenin effectively suppressed the proliferation of melanoma cells in vitro. Moreover, it inhibited cell migration and invasion, lengthened the dendrites, and induced G2/M phase arrest and apoptosis.
- Furthermore, apigenin promoted the activation of cleaved caspase-3 and cleaved PARP proteins and decreased the expression of phosphorylated (p)-ERK1/2 proteins, p-AKT and p-mTOR.
- Consequently, apigenin is a novel therapeutic candidate for melanoma.
- Apigenin inhibits proliferation and invasion, and induces apoptosis and cell cycle arrest in human melanoma cells. Oncol Rep. 2017 Apr;37(4):2277-2285. doi: 10.3892/or.2017.5450. Epub 2017 Feb 14. PMID: 28260058.

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Apigenin

- This study was designed for a comprehensive evaluation of Api as an antiproliferative, proapoptotic, antiangiogenic and immunomodulatory phytocompound.
- In the set experimental conditions, Api presents antiproliferative activity against the A375 human melanoma cell line, a G2/M arrest of the cell cycle and cytotoxic events as revealed by the lactate dehydrogenase release. Caspase 3 activity was inversely proportional to the Api tested doses, namely 30 µM and 60 µM. Phenomena of early apoptosis, late apoptosis and necrosis following incubation with Api were detected by Annexin V-PI double staining.
- The flavone interfered with the mitochondrial respiration by modulating both glycolytic and mitochondrial pathways for ATP production. The metabolic activity of human dendritic cells (DCs) under LPS-activation was clearly attenuated by stimulation with high concentrations of Api.
- Api elicited antiangiogenic properties in a dose-dependent manner.
- Comprehensive Assessment of Apigenin as an Antiproliferative, Proapoptotic, Antiangiogenic and Immunomodulatory Phytocompound. Nutrients. 2019 Apr 16;11(4):858. doi: 10.3390/nu11040858. PMID: 30995771; PMCID: PMC6521017.

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Apigenin is an Antiprolierative Protective Phytochemical

- Api has been studied intensively, and anticancer effects have been documented, with a possible efficacy for limiting cancer progression.
- Angiogenesis mediated anticancer activity is being reported in several studies, on various cancer types (e.g., lung cancer, prostate cancer, skin cancer, neuroblastoma, breast cancer) by modulating different pathways
- The effect was described for lung and colon cancer cells.
- Plant Flavone Apigenin: An Emerging Anticancer Agent. *Curr. Pharmacol. Rep.* 2017;3:423–446. doi: 10.1007/s40495-017-0113-2

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Apigenin

- The skin is the main barrier between the body and the environment, protecting it from external oxidative stress induced by ultraviolet rays. It also prevents the entrance of infectious agents such as viruses, external antigens, allergens, and bacteria into our bodies. An overreaction to these agents causes severe skin diseases, including atopic dermatitis, pruritus, psoriasis, skin cancer, and vitiligo.
- Members of the flavonoid family include apigenin, quercetin, luteolin, and kaempferol.
- Of these, apigenin has been used as a dietary supplement due to its various biological activities and has been shown to reduce skin inflammation by downregulating various inflammatory markers and molecular targets.
- Apigenin: A Therapeutic Agent for Treatment of Skin Inflammatory Diseases and Cancer. Int J Mol Sci. 2023 Jan 12;24(2):1498. doi: 10.3390/ijms24021498. PMID: 36675015; PMCID: PMC9861958.

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Parsley - CSCs

- **Background:** Petroselinum crispum (English parsley) is a common herb of the Apiaceae family that is cultivated throughout the world and is widely used as a seasoning condiment.
- In this study, P. crispum leaf and stem extracts were evaluated for their antioxidant properties, protection against DNA damage in normal 3T3-L1 cells, and the inhibition of proliferation and migration of the MCF-7 cells.
- **Results:** The dichloromethane extract of P. crispum exhibited the highest phenolic content (42.31 ± 0.50 mg GAE g(-1)) and ferric reducing ability (0.360 ± 0.009 mmol g(-1)) of the various extractions performed. The extract showed DPPH radical scavenging activity with an IC50 value of 3310.0 ± 80.5 µg mL(-1) . Mouse fibroblasts (3T3-L1) pre-treated with 400 µg mL(-1) of the extract showed 50.9% protection against H2 O2 -induced DNA damage, suggesting its potential in cancer prevention.
- The extract (300 µg mL(-1)) inhibited H2 O2 -induced MCF-7 cell migration by 41% ± 4%. As cell migration is necessary for metastasis of cancer cells, inhibition of migration is an indication of protection against metastasis.
- Petroselinum crispum has antioxidant properties, protects against DNA damage and inhibits proliferation and migration of cancer cells. J Sci Food Agric. 2015 Oct;95(13):2763-71. doi: 10.1002/jsfa.7078. Epub 2015 Feb 19. PMID: 25582089; PMCID: PMC5024025.

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Milk Thistle

- Silymarin (Silybum marianum; SM), popularly known as milk thistle, is an extract that has been used for many centuries to treat liver diseases.
- In recent years, several studies have shown that SM is not only just another antioxidant but also a multifunctional compound that exhibits several beneficial properties for use in the treatment and prevention of different types of pathologies and disorders.
- This review aims at demonstrating the main protective activities of SM in diseases, such as cancer, diabetes, hepatitis, non-alcoholic fatty liver disease, alcoholic liver disease, hepatitis C virus, hepatitis B virus, metabolic syndrome, depression, cardiovascular diseases and thalassemia, in addition to its photoprotective activity in in vitro tests and preclinical studies. Its main functions include antioxidant and anti-inflammatory effects, and it acts as modulator of signaling pathways.
- Signals ER beta
- Silymarin: not just another antioxidant. J Basic Clin Physiol Pharmacol. 2020 Mar 5;31(4):/j/jbcpp.2020.31.issue-4/jbcpp-2019-0206/jbcpp-2019-0206.xml. doi: 10.1515/jbcpp-2019-0206. PMID: 32134732.

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ER BETA

- ER Beta = controlled growth
- ER Alpha = growth
- Balance between two in local tissues, protects tissues

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Soy Isoflavones

- Signal ER beta

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Milk Thistle Signals ER Beta

- Silymarinmixture has been shown to contain a modest ligand for the βform estrogen receptor (ERβ).
- Erβ expression may serve to prevent breast cancer growth and serve as an antagonist to the mitogenic effects of ERα.
- Silymarin is a selective estrogen receptor beta (ERbeta) ago-nist and has estrogenic effects in the metaphysis of the femur but no or antiestrogenic effects in the uterus of ovariec-tomized (ovx) rats. J Steroid Biochem Mol Biol. 2003;86:179-188.

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Milk thistle – Anti-cancer agent

- Growing evidence suggests an antitumor and cardioprotective activity exerted by estrogen via its binding to estrogen receptor (ER) β.
- The aim of this study was to evaluate the anticancer activity of the phytoestrogen silibinin, an ERβ selective agonist, on DLBCL growth, and its potential cardioprotective effect.
- Materials and Methods: DLBCL cell lines SUDHL-8, SUDHL-6, and RIVA were used.
- The anti-tumor activity of silibinin was also evaluated in vivo in NOD/SCID/IL2Rg–/– (NSG) xenografted mice. AC16 human ventricular cardiomyocytes were used to investigate the cardioprotective effects of silibinin.
- Results: In vitro silibinin induced apoptosis and autophagy, and blocked tumor cell proliferation, also protecting AC16 cardiomyocytes from doxorubicin-induced toxicity. In vivo silibinin induced cell death and autophagy, and reduced tumor volume.
- Conclusion: Silibinin represents a promising therapeutic tool.
- The Natural Estrogen Receptor Beta Agonist Silibinin as a Promising Therapeutic Tool in Diffuse Large B-cell Lymphoma
- Anticancer Research February 2022, 42 (2) 767-779; DOI: https://doi.org/10.21873/anticanres.15535

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Milk Thistle – ER beta Ligand

- **Aim:** To assess the safety and effect of the supplementation of a patented blend of dietary phytoestrogens and insoluble fibers on estrogen receptor (ER)-β and biological parameters in sporadic colonic adenomas.
- **Methods:** A randomized, double-blind placebo-controlled trial was performed. Patients scheduled to undergo surveillance colonoscopy for previous sporadic colonic adenomas were identified, and 60 eligible patients were randomized to placebo or active dietary intervention (ADI) twice a day, for 60 d before surveillance colonoscopy. ADI was a mixture of 175 mg milk thistle extract, 20 mg secoisolariciresinol and 750 mg oat fiber extract. ER-β and ER-α expression, apoptosis and proliferation (Ki-67 LI) were assessed in colon samples.
- **Results:** No adverse event related to ADI was recorded. ADI administration showed a significant increases in ER-β protein (0.822 ± 0.08 vs 0.768 ± 0.10, P = 0.04) and a general trend to an increase in ER-β LI (39.222 ± 2.69 vs 37.708 ± 5.31, P = 0.06), ER-β/ER-α LI ratio (6.564 ± 10.04 vs 2.437 ± 1.53, P = 0.06), terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (35.592 ± 14.97 vs 31.541 ± 11.54, P = 0.07) and Ki-67 (53.923 ± 20.91 vs 44.833 ± 10.38, P = 0.07) approximating statistical significance. A significant increase of ER-β protein (0.805 ± 0.13 vs 0.773 ± 0.13, P = 0.04), mRNA (2.278 ± 1.19 vs 1.105 ± 1.07, P < 0.02) and LI (47.533 ± 15.47 vs 34.875 ± 16.67, P < 0.05) and a decrease of ER-α protein (0.423 ± 0.06 vs 0.532 ± 0.11, P < 0.02) as well as a trend to increase of ER-β/ER-α protein in ADI vs placebo group were observed in patients without polyps (1.734 ± 0.20 vs 1.571 ± 0.42, P = 0.07).
- **Conclusion:** The role of ER-β on the control of apoptosis, and its amenability to dietary intervention, are supported in our study.
- Phytoestrogens/insoluble fibers and colonic estrogen receptor β: randomized, double-blind, placebo-controlled study. World J Gastroenterol. 2013 Jul 21;19(27):4325-33. doi: 10.3748/wjg.v19.i27.4325. PMID: 23885143; PMCID: PMC3718900.

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Milk thistle

- Silymarin is a widely used standardized mixture of flavonolignans and its major component Silybinin binds to cytosolic estrogen receptors.
- Here, we demonstrate that this binding is exclusive to the estrogen receptor beta (ERbeta). Silymarin is a selective estrogen receptor beta (ERbeta) agonist and has estrogenic effects in the metaphysis of the femur but no or antiestrogenic effects in the uterus of ovariectomized (ovx) rats. J Steroid Biochem Mol Biol. 2003 Aug;86(2):179-88. doi: 10.1016/s0960-0760(03)00270-x. PMID: 14568570.

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Dandelion - controlled growth

- Certainly, dandelion has been used in traditional ethno-medicinal systems (i.e., Chinese, Arabian, Indian, and Native American) to treat different types of cancer.
- In the current study, the antiproliferative activity of methanolic extracts of dandelion root (MEDr) on cell viability of HepG2, MCF7, HCT116, and normal Hs27 was investigated.
- It was observed that MEDr (500 µg/mL) drastically decreased the growth of HepG2 cell line, while the effect on MCF7 and HCT116 cell lines was less pronounced and no effect has been observed in Hs27 cell lines. The MEDr also enhanced the phosphorylation level of AMPK of HepG2 cells, which considered crucial in cancer treatment and other metabolic diseases. The AMPK activation by MEDr noticed in the current study has never been reported previously. The results regarding the number of apoptotic cells (HepG2 cells) were in line with the cell viability test. The current observations clearly demonstrated the potency of MEDr against liver cancer with validation that dandelion could control AMPK and thus cancer in the treated cell lines.
- Effect of Methanolic Extract of Dandelion Roots on Cancer Cell Lines and AMP-Activated Protein Kinase Pathway. Front Pharmacol. 2017 Nov 28;8:875. doi: 10.3389/fphar.2017.00875. PMID: 29234282; PMCID: PMC5712354.

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Dandelion Root Extract (DRE)

- Dandelion extracts have been studied extensively in recent years for its anti-depressant and anti-inflammatory activity. Recent work from our lab, with *in-vitro* systems, shows the **anti-cancer potential of an aqueous dandelion root extract (DRE) in several cancer cell models, with no toxicity to non-cancer cells.**
- In this study, we examined the cancer cell-killing effectiveness of an aqueous DRE in colon cancer cell models. Aqueous DRE induced programmed cell death (PCD) selectively in > 95% of colon cancer cells, irrespective of their p53 status, by 48 hours of treatment.
- The anti-cancer efficacy of this extract was confirmed in *in-vivo* studies, as the **oral administration of DRE retarded the growth of human colon xenograft models by more than 90%.**
- We found the activation of multiple death pathways in cancer cells by DRE treatment, as revealed by gene expression analyses showing the expression of genes implicated in programmed cell death. Phytochemical analyses of the extract showed complex multi-component composition of the DRE, including some known bioactive phytochemicals such as α-amyrin, β-amyrin, lupeol and taraxasterol. This suggested that this natural extract could engage and effectively target multiple vulnerabilities of cancer cells.
- Therefore, DRE could be a non-toxic and effective anti-cancer alternative, instrumental for reducing the occurrence of cancer cells drug-resistance.
- Dandelion root extract affects colorectal cancer proliferation and survival through the activation of multiple death signalling pathways. Oncotarget. 2016 Nov 8;7(45):73080-73100. doi: 10.18632/oncotarget.11485. PMID: 27564258; PMCID: PMC5341965.

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Dandelion Root Extract

- In this study, we show that dandelion root extract (DRE) specifically and effectively suppresses proliferation and migration in human gastric cells without inducing toxicity in noncancerous cells.
- Long noncoding RNAs (lncRNAs) are known to promote tumorigenesis in many cancer types.
- Here, we showed that the lncRNA colon cancer-associated transcript-1 (CCAT1) was down-regulated in dandelion-treated GC cells.
- Furthermore, downregulation of CCAT1 inhibited proliferation and migration of gastric cells.
- We also found that DRE exerted its function in GC cells partially through targeting CCAT1.
- Dandelion root extract suppressed gastric cancer cells proliferation and migration through targeting lncRNA-CCAT1. Biomed Pharmacother. 2017 Sep;93:1010-1017. doi: 10.1016/j.biopha.2017.07.007. Epub 2017 Jul 14. PMID: 28724210.

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Dandelion Blocks CSCs in BC

- Introduction:
- Breast cancer stem cells (BCSCs) play an important role in breast cancer initiation, metastasis, recurrence, and drug resistance. Therefore, targeting BCSCs is an essential strategy to suppress cancer growth. This study aimed to evaluate the effects of dandelion *Taraxacum officinale* extracts on BCSC proliferation *in vitro* in 2D and 3D cell culture platforms.
- Methods:
- The BCSCs were maintained understandard conditions, verified for expression of CD44 and CD24 surface markers, and transfected with GFP before use in experiments. In the 2D model, the BCSCs were cultured as adherent cells in standard culture plates; in the 3D model, the BCSCs were cultured on low-adherent plates to form spheroids. The effect of Dandelion extracts on proliferation of BCSC was assessed by evaluating induction of cell death, expression of genes of death receptor signaling pathways, and production of reactive oxygen species (ROS) by BCSCs.
- Conclusion:
- Dandelion extracts are promising extracts for the treatment of breast tumors. The effect of methanol dandelion extract was better than that for ethanol extract. Importantly, BCSCs in 3D exhibited stronger drug resistance than those in 2D. In summary, our results indicate the strong potential of dandelion extracts as anti-cancer agents and rational use for drug development.
- Taraxacum officinale dandelion extracts efficiently inhibited the breast cancer stem cell proliferation *Biomedical Research and Therapy* **volume 3**, Article number: 34 (2016)

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Human Transforming Growth Factor Beta1 TGFB1 – Boosts CSC renewal?

- When elevated.
- Transforming growth factor-β (TGFβ), are involved in stem cell renewal, differentiation, survival, and are commonly deregulated in HCC.
- Control of stem cell proliferation by the TGFβ, Notch, Wnt and Hedgehog pathways to
- suppress hepatocellular cancer and to form the endoderm suggest a dual role for this pathway in
- tumor suppression as well as progression of differentiation from a stem or progenitor stage.
- Cancer stem cells and hepatocellular carcinoma Cancer Biol Ther. 2009 September ; 8(18): 1691–1698.

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TGFB1 – Gut, Biliary, Liver Cancer (also marker of mold exposure)

- The TGFβ signaling pathway appears to be most prominent at the interface between development and cancer in liver and gut epithelial cells.
- Drives transition of stem cells into fully cancer promoting cells.
- Especially in the gut,biliary duct and liver.

- Cancer stem cells and hepatocellular carcinoma Cancer Biol Ther. 2009 September ; 8(18): 1691–1698.

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TGFB1 – drives all fibrosis – Blocked by Taurine (anti-fibrinogenic)

- The cell strain M, which was established from normal rat liver cells, is characterized by the active formation of a collagen fiber network. In this study, we investigated the characterization of M cells and evaluated the anti-fibrogenic effects of taurine using this culture system.
- Also, M cells expressed transforming growth factor (TGF)-beta1, -beta2, and TGF-beta type I and II receptors, and treatment with TGF-beta1 (1ng/ml) for 6 days markedly stimulated the formation of a collagen fiber network and expression of procollagen alpha1(I) mRNA.
- When M cells were treated with various concentrations of taurine (10-50mM), network formation and procollagen alpha1(I) expression were significantly suppressed in a dose dependent manner.
- **Additionally**, **even in the presence of TGF-beta1**, **taurine treatment effectively reduced the formation of a collagen fiber network**.
- These results suggest that M cells exhibit features of not only hepatocytes but also myofibroblasts, and TGF-beta1 plays an important role in the formation of collagen fiber networks in this culture system. Additionally, this M cell culture system is appropriate for use as an in vitro model of hepatic fibrosis in the evaluation of the anti-fibrogenic effects of various agents.
- Transforming growth factor-beta-induced stimulation of formation of collagen fiber network and anti-fibrotic effect of taurine in an in vitro model of hepatic fibrosis. Hepatol Res. 2004 Sep;30(1):34-41. doi: 10.1016/j.hepres.2004.04.006. PMID: 15341772.

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Taurine – TGFB1

(Receptor Detox + Hormone B & P = 30 mg of full flush niacin)

- Regulation by Taurine + Niacin
- We have reported that taurine (T) and niacin (N) inhibit the expression of procollagen type I and type III genes at the level of gene transcription in the bleomycin (BL) hamster model of lung fibrosis.
- In the present study, we have investigated the effects of TN in diet on the temporal expression of transforming growth factor-beta1 (TGF-beta1) mRNA and TGF-beta1 protein production in the same model of lung fibrosis to determine whether the decreased transcription of procollagen genes is associated with downregulation of TGF-beta1 mRNA. Our results demonstrate that expression of TGF-beta1 mRNA in lungs is increased in BL-treated hamsters in the BL + control diet (CD) group, compared to saline controls in the saline-instilled (SA) + CD group, by 3.5-, 2.5-, 4-, and 2-fold at 3, 7, 14, and 21 d, respectively, and TN treatment caused significant decreases in TGF-beta1 mRNA expression in BL-treated animals in the BL + TN group from Day 3 through Day 21. In addition, TN treatment also reduced TGF-beta1 protein in bronchoalveolar lavage fluid (BALF) from BL-treated animals in the BL + TN group. These decreases in TGF-beta1 mRNA and TGF-beta1 protein correlated with decreased lung collagen content in hamsters in the BL + TN group as demonstrated in our earlier study. To confirm that the TGF-beta1 activity observed in BALF is reflected at the transcriptional level, total RNA was isolated from lavaged cells. Reverse transcriptase-polymerase chain reaction analysis demonstrated maximal expression of TGF-beta1 mRNA transcripts in BL-treated lavaged cells from animals in the BL + CD group and only low levels were detected in both saline control groups, and in BL + TN-treated lavaged cells. Nuclear runoff analysis indicated that TN-mediated reduction of TGF-beta1 mRNA steady-state levels was a result of decreased gene transcription, suggesting a transcriptional downregulation mechanism.
- Our results indicate that the combined treatment with TN ameliorates BL-induced lung fibrosis, at least in part, via inhibition of TGF-beta1 mRNA expression.
- Regulation of transforming growth factor-beta1 mRNA expression by taurine and niacin in the bleomycin hamster model of lung fibrosis. Am J Respir Cell Mol Biol. 1998 Mar;18(3):334-42. doi: 10.1165/ajrcmb.18.3.2867. PMID: 9490651.

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Fibrosis – Drives Adverse Tissue Remodeling

- Sulforophanes in Hormone Balance and Protect
- Antifibrotic therapies aim to inhibit the accumulation of fibrogenic cells and/or prevent the deposition of extracellular matrix proteins.
- Natural products from terrestrial and marine sources, including sulfur-containing compounds, exhibit promising activities for the treatment of fibrotic pathology.
- Natural Sulfur-Containing Compounds: An Alternative Therapeutic Strategy against Liver Fibrosis. Cells. 2019 Oct 30;8(11):0. doi: 10.3390/cells8111356. PMID: 31671675; PMCID: PMC6929087.

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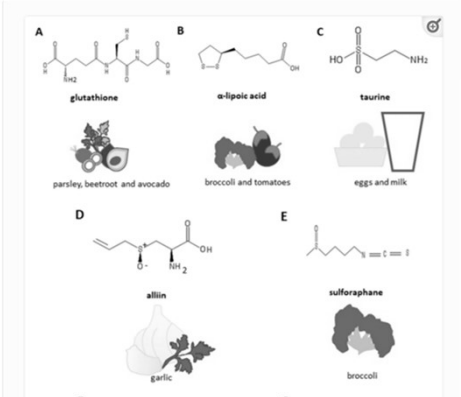
Anti-fibrinolytics



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Taurine

- **Background and aim:** The mechanism of pancreatic fibrosis is unclear. Taurine is used in the clinical treatment of a wide variety of diseases, but its effect on improving pancreatic fibrosis is unknown. We examined whether a diet with added taurine improves pancreatic fibrosis induced by dibutyltin dichloride (DBTC) in an experimental chronic pancreatitis rat model. In addition, we examined the influence of taurine on pancreatic stellate cells.
- **Methods:** Pancreatic fibrosis was induced by DBTC. Rats were fed a taurine-containing diet or a normal diet and were killed at 4 weeks. Pancreatic stellate cells were isolated from male Wistar rats. Cultured pancreatic stellate cells were incubated with or without taurine chloramine. Type I collagen and transforming growth factor-beta1 secretion was evaluated by ELISA, and matrix metalloproteinase activity was assessed by gelatin zymography. Interleukin-6, interleukin-2, and transforming growth factor-beta1 levels in the supernatants of pancreatic tissue homogenates were measured.
- **Results:** Pancreatic fibrosis induced by DBTC was improved remarkably by the oral administration of the taurine-containing diet.
- **Taurine chloramine decreased type I collagen, transforming growth factor-beta1, and matrix metalloproteinases 2 of the pancreatic stellate cell culture supernatant**.
- **Conclusion:** The oral administration of taurine improves pancreatic fibrosis. Taurine chloramine inhibits transforming growth factor-beta1 produced from activated pancreatic stellate cells and improves pancreatic fibrosis.
- Oral administration of taurine improves experimental pancreatic fibrosis. J Gastroenterol Hepatol. 2008 Feb;23(2):321-7. doi: 10.1111/j.1440-1746.2007.05127.x. Epub 2007 Aug 30. PMID: 17764527.

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Taurine – normalizes all stages of non-alcoholic fatty liver

- Our objective was to explore the restorative effect of taurine on experimental nonalcoholic steatohepatitis (NASH).
- Thirty-six SD rats were randomly divided into three groups, 12 in each group: the normal group was fed standard rat diet; the model group and the treatment group were both fed a high-fat rat diet for 12 weeks, and the rats in the treatment group were simultaneously injected with taurine subcutaneously for 8 weeks. Hepatic histological change was observed; TNF-alpha and TGF-beta(1) protein expression was identified by immunohistochemistry; mRNA expression of TNF-alpha, TGF-beta(1), type I procollagen, and adiponectin was measured by RT-PCR; body weight, weight gain, liver weight, and liver index were measured; and biochemical parameters monitored included serum transaminases, serum lipids, fasting plasma glucose, and hepatic level of oxidative stress. Rats in the model group showed a significant increase in liver weight, liver index, serum transaminase activities, serum triglyceride, fasting plasma glucose, and oxidative stress; the mRNA expression of TNF-alpha, TGF-beta(1), and type I procollagen increased, whereas the expression of adiponectin decreased significantly, compared with that in the normal group. The typical hepatic lesions of NASH were observed histologically in the model group.
- Taurine treatment resulted in a significant decrease in liver weight, liver index, serum transaminase activities, serum triglyceride, fasting plasma glucose, and oxidative stress; the mRNA expression of TNF-alpha, TGF-beta(1), and type I procollagen decreased, but the expression of adiponectin increased significantly, compared with that in the model group.
- Histological improvement was observed in the treatment group.
- **In conclusion, taurine could inhibit lipid peroxidation, improve lipid and glucose metabolism, decrease synthesis of TNF-alpha and TGF-beta(1), promote synthesis of adiponectin, and have a restorative effect on experimental NASH.**
- The restorative effect of taurine on experimental nonalcoholic steatohepatitis. Dig Dis Sci. 2006 Dec;51(12):2225-34. doi: 10.1007/s10620-006-9359-y. Epub 2006 Nov 2. PMID: 17080243.

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