

# Integrative Oncology: Plant Products

Printed from <https://www.cancerquest.org/patients/integrative-oncology/plant-products> on 12/22/2024

**Before** reading about plant-based complementary treatments, please see the following:

- [Introduction on Integrative Oncology](#)
- [Note on Complementary Approaches](#)
- [Introduction to Scientific Research](#)

Many different plant products have been studied for their ability to prevent and/or treat cancer. The list below is not meant to be complete, but it does include some of the plant products studied for these activities.

Because the active chemicals in plants that seem to help prevent cancer are often the same ones that help fight cancer once it has developed, we have combined those two activities in the following descriptions.

**The following plant-based treatments have shown activity in animal models (*n vivo*) or with human cells in the lab (*n vitro*) as a cancer treatment. Read the individual entries for prevention information.**

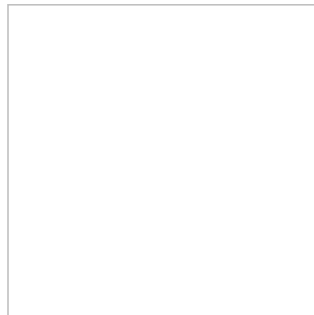
- [Anthocyanin \(Berries\)](#)
- [Bromelain \(Pineapples\)](#)
- [Curcumin \(Turmeric\)](#)
- [EGCG \(Green Tea\)](#)
- [Lycopene \(Tomatoes\)](#)
- [Phytoestrogens \(Soy\)](#)
- [Pycnogenol \(Pine Trees\)](#)
- [Resveratrol \(Grapes\)](#)
- [Selenium \(Nuts\)](#)

**The following plant-based treatments DO NOT have substantial scientific support in any model as a cancer treatment.**

- [Cannabis and Hemp Oil \(Cannabis\)](#)
- [Essiac<sup>®</sup>, Flor-Essence<sup>®</sup> \(mixture\)](#)
- [Gerson Therapy \(Mixture\)](#)
- [Graviola/Soursop](#)

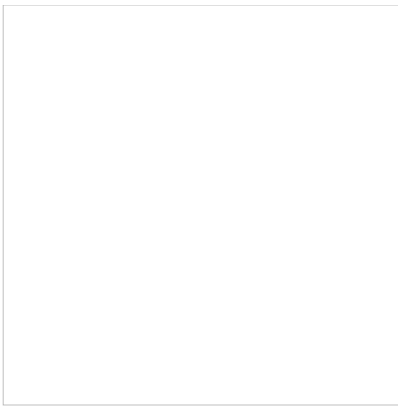
---

## Anthocyanin



### Classified as:

Phytochemical, Polyphenol, Flavonoid, Anthocyanidin



Structure of Anthocyanin

### Intro and Background

The term anthocyanin refers to a group of compounds found in vegetables, citrus fruits, red wine, and especially in edible berries. Anthocyanins are responsible for the red, blue, and purple colors of many plants. [1](#) They may help prevent cardiovascular disorders, age complications, obesity, inflammatory responses, cancer, and other degenerative diseases.[2](#) [1](#) These compounds also exhibit antioxidant behavior\* which can help protect DNA and its structure.[2](#) Anthocyanins leave the body quickly after they are eaten, and it is not currently known where and how quickly they are absorbed. [1](#) These types of compounds may fight cancer by inducing [apoptosis](#) and inhibiting [proliferation](#) of cancer cells. [3](#)

### Scientific Research

Studies have shown that anthocyanins can slow the growth of tumor cells *in vitro*.[4](#) [5](#) [6](#) [7](#) Because it is unclear how anthocyanins will act in animal experiments, [8](#) no clinical trials seem to have been performed to investigate the ability of anthocyanins to treat cancer in humans. Most of the recent research seems to be focused on the ability of anthocyanins to prevent cancer rather than treat it. Anthocyanins do not seem to have side effects in studies done on cells *in vitro*. [9](#)

Currently, a [trial](#) investigating the ability of anthocyanin to modulate the side effects of radiation in breast cancer patients is recruiting participants.[10](#) For information about ongoing clinical trials involving anthocyanins, please visit our section on [Finding Clinical Trials](#).

### US Food and Drug Administration Approval

There is not enough evidence to support the effectiveness of anthocyanins in the fight against cancer, and they have not been approved by the FDA for cancer treatment. [11](#)

\*It is important to keep in mind that many cancer treatments, including chemotherapy and radiation, work by generating free radicals in order to destroy cancer cells. If a cancer patient takes antioxidants while undergoing radiation or chemotherapy treatment, it is possible that these compounds may protect tumor cells from the desired free radicals. Doctors may recommend that patients undergoing these treatments avoid antioxidants so that the treatment is as effective as possible. [12](#)

---

## Bromelain

### Classification

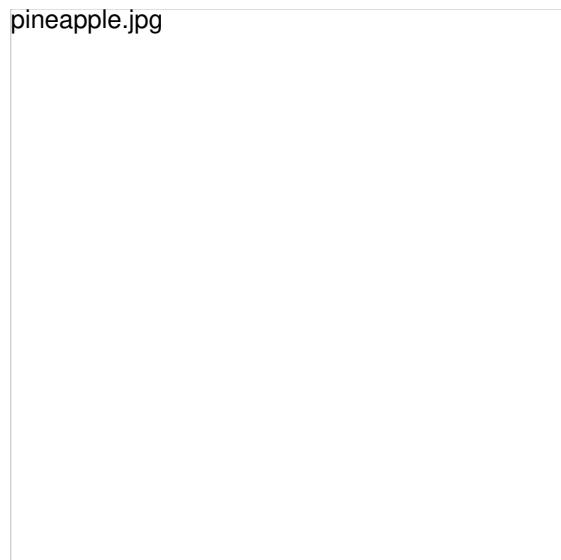
As a phytochemical, the term "bromelain" collectively denotes enzymes, or catalytic polymers of amino acids, found in the Bromeliaceae plant family, whose most recognized member is the pineapple.[13](#) Technically, pineapple stem bromelain is not the same enzyme as pineapple fruit bromelain, [13](#) though in practice both are referred to as bromelain.

### Intro and Background

Pineapple has long been used therapeutically in South America and Southeast Asia[14](#) and was called in 1558 "the fruit of which the natives of America make the greatest medicinal use."[15](#) Although bromelain was isolated as the active enzyme in pineapple in 1891,[15](#) it was not commercially produced because pineapple was relatively expensive. However, in 1957 Heinecke discovered that the discarded stem contains more bromelain than the fruit,[13](#) paving the way for bromelain's production as a medicinal compound. Today, nutrition stores throughout America sell it as a supplement that supports digestion,[16](#) though it has multiple biological uses.

### Scientific Research

Bromelain has been studied for decades. Not only does it potentially fight inflammation,[14](#) a major contributor to cancer,\* but it also exhibits anti-cancer activity both in cell culture (*in vitro*) and in mouse models (*in vivo*), blocking growth and causing death of cancer cells.[17](#) So, the way in which bromelain stops cancer is known[18](#) The enzymes in bromelain are proteolytic; they can break down proteins on the surfaces of cells, influencing cell signaling and behavior. Nonetheless, not all of bromelain's biological activity can be attributed to proteolysis.[13](#)



Pineapple on plant and sliced (Wikimedia Commons)

Large amounts of bromelain must reach a tumor site for significant results.[18](#) Even though human beings tolerate bromelain at relatively high doses without side effects,[16](#) it is very difficult to get the required levels of the chemical in the body. As a result, studies are currently underway to investigate nanoparticle delivery of bromelain.[18](#)

#### **Clinical Trials**

A clinical trial exploring the efficacy of bromelain as an anti-cancer treatment has been initiated.[19](#) Another study investigated the use of bromelain, in conjunction with other compounds, to reduce the side effects associated with chemotherapy, but its results are not available.[20](#)

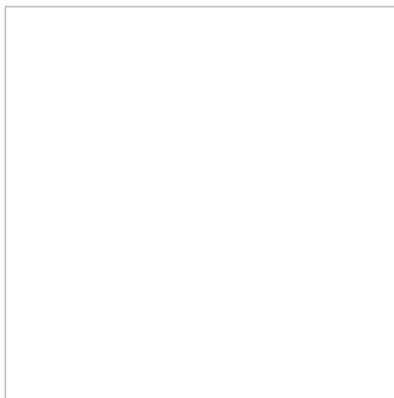
#### **US Food and Drug Administration Approval**

There is not enough evidence that bromelain treats cancer, and bromelain has not been approved by the FDA for cancer treatment.[21](#)

\*For more information, see our [Inflammation](#) section.

---

## **Curcumin**



#### **Classified as:**

Phytochemical, Polyphenol

#### **Also called:**

Diferuloylmethane



Structure of Curcumin

## Intro and Background

Curcumin comes from the turmeric plant (*Curcuma longa*). It is responsible for the yellow color of curry, a traditional spice used in Southeast Asian cuisine and medicine. [22](#)

This agent has been used for centuries by different cultures in Asia. For example, Indian medicinal practices have used curcumin to treat anorexia, cough, rheumatism, and other diseases. [23](#) Hindu medicine men still use curcumin to treat sprains and swelling. [23](#) Traditional Chinese medicine uses this same compound to treat diseases that are accompanied by abdominal pain. [23](#) Western medicine has recently recognized that curcumin may have anti-inflammatory, antioxidant\*, anti-bacterial, anti-venom, and anti-HIV activity, as well as the ability to combat Alzheimer's disease. [23 24](#)

In terms of cancer fighting ability, curcumin may induce apoptosis while reducing [angiogenesis](#), [metastasis](#), [proliferation](#), transformation,[25](#) and [epithelial-to-mesenchymal transition](#).[26](#)

[Watch the full interview with Dr. Dennis Liotta](#) an Emory researcher working with curcumin to develop cancer prevention and treatment drugs.

## Scientific Research

### *Pre-Clinical/Laboratory Studies*

Curcumin has been found to slow tumor cell development [27](#) and angiogenic processes [28](#) *in vitro* and in rodent experiments. Also, curcumin seems to induce [apoptosis](#) in cancer cells without hurting healthy ones. [29](#) Both *in vitro* (cancer cell lines) and *in vivo* (animals) studies show that it has anti-tumor effects in melanoma[26](#) breast cancer,[30](#) colon cancer,[31 32](#) pancreatic cancer,[26 33](#) and head and neck cancer,[32](#) among others.

Curcumin may also increase the efficacy of standard cancer treatments. For example, as a blocker of the pro-inflammatory protein NF-kB, curcumin has the potential to prevent cells from becoming resistant to chemotherapy.[34](#) As for radiation, pre-clinical evidence, or research done in the laboratory but not in humans, suggests that curcumin can prime cancerous cells to death by radiation and protect normal cells against death by radiation.[35](#)

In June of 2017 a study was published which examined different combinations of nutrients on mouse prostate cancer cells, both in culture and in animals. Curcumin showed positive results in these studies. [36 37](#)

In August 2018, one of curcumin's main hurdles to use in humans was overcome. Curcumin does not dissolve well in water or fat and is therefore hard to get into the body in amounts that are helpful. Research at the University of Illinois were able to combine

a platinum-based chemotherapy drug with curcumin in a way that greatly increased the activity of the combined drug against cancer cell lines. The technique needs additional work and testing in animals before it can move to human patients, but is a great step forward.[38](#)

#### *Clinical Trials/Studies with Humans*

With laboratory studies establishing it as a promising agent in the fight against cancer, curcumin has drawn the attention of many researchers. Over 50 clinical trials are currently investigating its ability to treat and prevent cancer, either alone or in combination with other treatments. Most of these trials are ongoing, and their results have not been posted.[39](#)

Curcumin has been demonstrated to be safe taken in pill form in conjunction with chemotherapy[40](#). As for the side effects of cancer therapy, taking curcumin orally was found to significantly decrease the "burning" (technically, radiation dermatitis and moist desquamation) of the skin associated with radiation treatment,[41](#) [42](#) though a larger study found no statistically significant improvement.[43](#)

Curcumin has run into several problems in clinical trials because it has poor bioavailability (i.e. it has difficulty working and staying inside the human body).[26](#) [44](#) Researchers are working on stabilizing the molecule via nanotechnology and chemical approaches.[26](#) [30](#) [44](#) More bioavailable curcumin analogues have also been made.[40](#)

For information about ongoing clinical trials involving curcumin, please visit our section on [Finding Clinical Trials](#).

[Find clinical trials at the Winship Cancer Institute of Emory University](#)

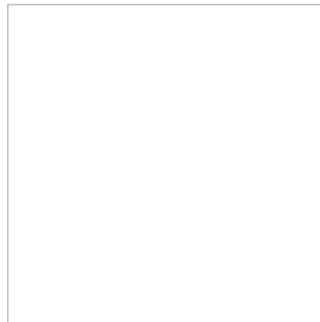
#### **US Food and Drug Administration Approval**

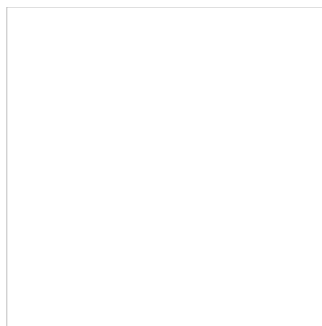
There is not enough evidence that curcumin effectively kills cancerous cells, and it has not been approved by the FDA for cancer treatment. [11](#) In fact, a number of curcumin products are on the [FDA's list of Fake Cancer "Cures."](#)

\*It is important to keep in mind that many cancer treatments, including chemotherapy and radiation, work by generating free radicals in order to destroy cancer cells. If a cancer patient takes antioxidants while undergoing radiation or chemotherapy treatment, it is possible that these compounds may protect tumor cells from the desired free radicals. Doctors may recommend that patients undergoing these treatments avoid antioxidants so that the treatment is as effective as possible. [12](#)

---

## **EGCG**

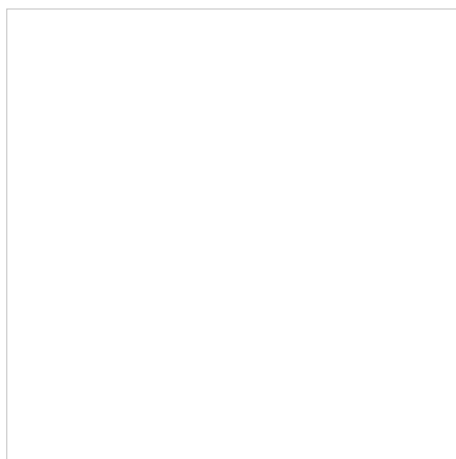


**Classified as:**

Phytochemical, Polyphenol

**Also called:**

epigallocatechin-3-gallate



Structure of EGCG

**Intro and Background**

Tea is one of the most widely consumed beverages on the planet, second only to water. [45](#) Green tea comes from the plant *Canellia sinesis*, an evergreen shrub of the *Theaceae* family. Green, black, and oolong teas all come from this same plant but differ in the way they are prepared. [46](#) Because it is not allowed to ferment, green tea retains many of the beneficial properties of the tea plant. In general, many plants produce chemicals called polyphenols that protect them from environmental damage. The polyphenol EGCG (epigallocatechin-3-gallate) is present in large amounts in green tea. [45](#) EGCG has antioxidant properties and has shown to have some preventative effects against skin, lung, esophagus, stomach, liver, small intestine, pancreas, colon, bladder and breast cancers. [47](#) [48](#) Worldwide, tea is believed to have a number of beneficial effects varying from improving blood flow, eliminating toxins, increasing resistance to diseases, increasing cardiovascular health, lowering cholesterol and preventing/combating cancer. Green tea has been found to have antioxidant\* and health promoting benefits due mostly to its higher content of epigallocatechin-3-gallate (EGCG). [45](#)

**Scientific Research**

Studies involving large populations of people suggest that drinking green tea may be associated with a lower risk of some cancer types. [49](#)

These findings have been a basis for research into the cancer-fighting abilities of green tea. EGCG has been found to prevent cancer cells from getting nutrients ([angiogenesis](#)), [50](#) cause cancer cells to die ([apoptosis](#)), [51](#) stop cancer cells from traveling, [51](#) prevent tumors from growing, [51](#) and inhibit cellular [proliferation](#). [52](#) [51](#) Moreover, EGCG exerts these effects on cancerous cells, not normal cells, [51](#) making it very safe.

There have been numerous clinical trials to determine the ability of EGCG to prevent cancer with mixed results. One study found that it decreased oxidation and NF-kB, an important protein for inflammation, in cancerous prostatic tissue, but it did not significantly affect apoptosis or proliferation. [53](#) In breast cancer patients, EGCG did not significantly decrease VEGF and HGF, markers of angiogenesis and proliferation. [54](#) but in prostate cancer patients, it did, according to another study. [55](#) Many other studies are ongoing; for example, one is investigating how well green tea extract can treat bladder cancer patients. [56](#)

Drinking tea (and coffee) has been shown to cause epigenetic changes in women (but not men). Interestingly, many of the changes were found in genes that function in cancer and hormone (estrogen) metabolism. The reason for the sex-specific effects are not known, but could be due to activities of sex hormones. [57](#)

Learn more about [angiogenesis](#), [apoptosis](#), [metastasis](#) and [proliferation](#).

### **US Food and Drug Administration Approval**

There is not enough evidence that EGCG is effective in the fight against cancer, and it has not been approved by the FDA for cancer treatment. [58](#)

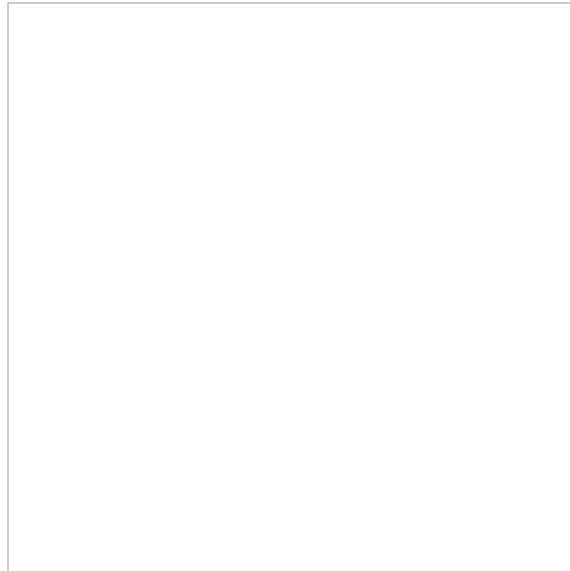
\*It is important to keep in mind that many cancer treatments, including chemotherapy and radiation, work by generating free radicals in order to destroy cancer cells. If a cancer patient takes antioxidants while undergoing radiation or chemotherapy treatment, it is possible that these compounds may protect tumor cells from the desired free radicals. Doctors may recommend that patients undergoing these treatments avoid antioxidants so that the treatment is as effective as possible. [12](#)

---

*Please be sure to see our [notice on complementary therapies](#). To better understand and evaluate the research described above, read our [Introduction to Scientific Research](#).*

---

## **Lycopene**



### **Classification**

Phytochemical, Carotenoid



Structure of Lycopene

## Intro and Background

Lycopene is the compound that gives tomatoes (*Solanum lycopersicum*) their red color.<sup>59</sup> Watermelon, grapefruit, guava, and papaya also contain lycopene but in lower amounts than tomatoes. Consumption of this antioxidant\* has long been associated with a decreased risk of prostate cancer.<sup>60</sup> Most research about lycopene and cancer involves prostate [cancer prevention](#). Studies have also suggested that lycopene is more effective when it is ingested from a tomato, as opposed to a supplement.<sup>61</sup>

## Scientific Research

Results of *in vitro* tests are encouraging. For example, treatment with Racimo, a kind of tomato high in lycopene, stopped colorectal cancer cells from growing,<sup>62</sup> and when prostate cancer cells were treated with lycopene, [apoptosis](#) was induced in a significant number of cells.<sup>63</sup> Lycopene was also shown to inhibit the growth of prostate cancer cells *in vivo*.<sup>64</sup> This may occur through increased expression of an enzyme called BCO2, a tumor suppressor that decreases NF-kB activity.<sup>65</sup> However, lycopene was only observed to increase BCO2 expression in cells that relied on male hormones for growth (termed "androgen-sensitive").<sup>65 66</sup>

Lycopene also has supportive results from *in vivo* tests. For example, in a study involving rats, tomato powder inhibited the creation of cancer cells, prolonged the animals' survival, and reduced animal death rates.<sup>67</sup>

Lycopene is the focus of many phase II clinical trials investigating its ability to both prevent and treat prostate cancer. Though some completed trials have published results, the results are either not strong or not generalizable.<sup>68 69 61</sup>

One trial comparing how well tomato juice and tangerine juice can stop prostate cancer from progressing is recruiting participants.<sup>70</sup> For information about ongoing clinical trials involving lycopene, please visit our section on [Finding Clinical Trials](#).

In summary, though pre-clinical evidence is favorable, there is not enough evidence to decide whether lycopene can treat cancer effectively in humans.

Learn more about [apoptosis and cancer](#).



### For Further Reading

The National Cancer Institute has published a Physician Data Query (PDQ) summary of prostate cancer, which includes [a section on lycopene](#).

### US Food and Drug Administration Approval

There is not enough evidence that lycopene is effective in the fight against cancer, and it has not been approved by the FDA for cancer treatment. [11](#) In fact, one lycopene product is on the [FDA's list of Fake Cancer "Cures."](#)

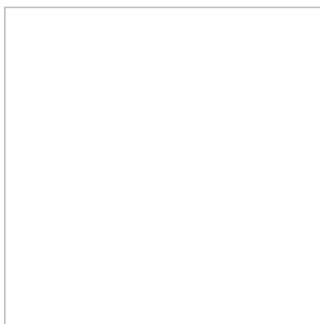
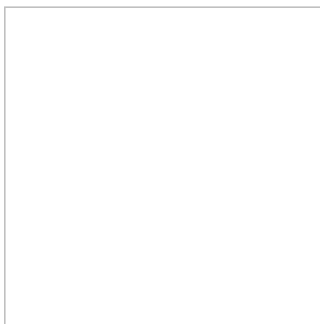
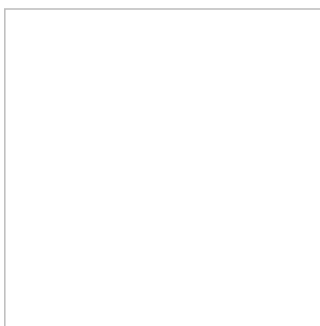
\*It is important to keep in mind that many cancer treatments, including chemotherapy and radiation, work by generating free radicals in order to destroy cancer cells. If a cancer patient takes antioxidants while undergoing radiation or chemotherapy treatment, it is possible that these compounds may protect tumor cells from the desired free radicals. Doctors may recommend that patients undergoing these treatments avoid antioxidants so that the treatment is as effective as possible. [12](#)

---

*Please be sure to see our [notice on complementary therapies](#). To better understand and evaluate the research described above, read our [Introduction to Scientific Research](#).*

---

## Phytoestrogens

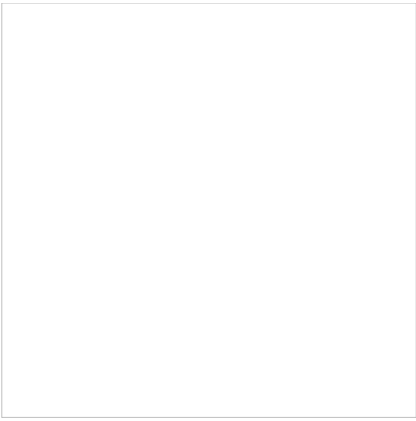


### Classified as

Phytochemical, Phytoestrogens, Isoflavone

### Types of Phytoestrogens

Isoflavones (e.g. genistein, daidzein, glycitein, formononetin) [71](#)



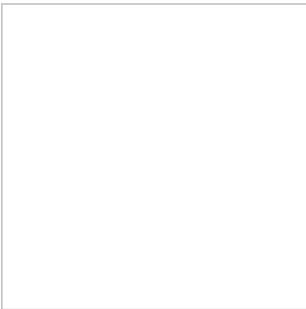
Structure of Genistein

,



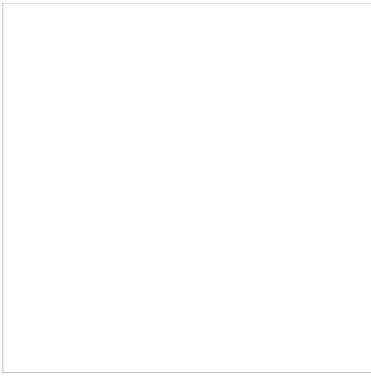
Structure of Daidzein

Lignans (e.g. secoisolariciresinol, matairesinol, pinoresinol, lariciresinol) [71](#)



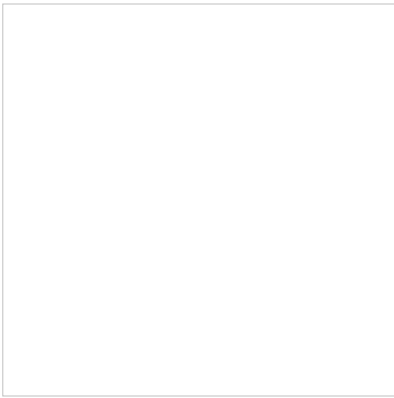
Structure of Lignan

Coumestan (e.g coumestrol) [72](#)



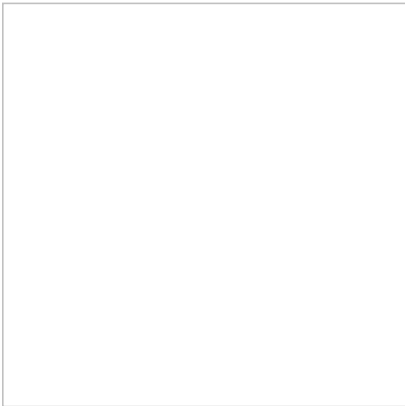
Structure of Coumestran

Isoflavonoids

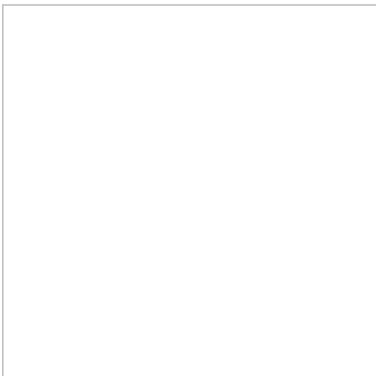


Structure of Isoflavonoids

Flavonoids (flavanols, flavanones, flavones, flavonols) [72](#)



Structure of Flavonol



## Intro and Background

The term phytoestrogen classifies a large group of compounds derived from plants and naturally found in many foods. Major groups of phytoestrogens are isoflavones, lignans and coumestans. Isoflavones are most commonly found in soy, legumes, meat, cereals, nuts, fruits, and vegetables. Lignans are found in most plants with flaxseed registering the highest concentrations.[71](#) Coumestans can be found in pinto beans, alfalfa sprouts, and vegetables.[73](#)

Phytoestrogens have been found to exhibit antioxidant\* properties.[74](#) Because antioxidant activity is associated with the health and survival of cells, this discovery has led some to believe that they may be able to prevent and combat cancer in humans.[75](#) Another reason phytoestrogens are believed to be anticancer agents is the lower occurrence of prostate and breast cancer in Asian nations. In these countries, much more phytoestrogens from soy and vegetables are consumed than in Western countries. This intake, presumably, contributes to their low rate of these cancer types.[76](#)

These compounds are also assumed to inhibit cancer growth because they have structural similarity to steroid hormones like estrogen and testosterone. Estrogen is a known instigator of hormone responsive cancer types, like breast, uterine, endometrial cancers. The resemblance of phytoestrogens to estrogen allows them to bind to molecular receptors intended for this hormone, preventing the hormones from binding and resulting in fewer cancer-causing signals in cells.[77](#) Researchers believe that this class of compounds may also be involved in regulating cell death ([apoptosis](#)) as well.[74](#) Phytoestrogens are also being studied for their potential to protect against cardiovascular disease, osteoporosis, and menopausal symptoms.[71](#)

## Scientific Research

While older population studies from the early and mid-nineties suggest that a diet higher in phytoestrogens may reduce hormone-related cancers, recent studies have yielded conflicting results about the effectiveness of phytoestrogens against cancer.[78](#)

Phytoestrogens can hinder [metastasis](#),[79](#) a key to cancer progression. According to one study, high doses of a phytoestrogen from soy (genistein) can slow down the growth of mouse cancer cells *in vitro*.[80](#) In another study, a combination of soy phytoestrogens (genistein and daizein, pictured above, plus glycitein) was shown to stop prostate cancer cells from growing in another *in vitro* assay.[81](#) Another research group concluded that coumestrol, pictured above, caused cancer cell death by interacting with copper, of which cancer cells contain high levels, and damaging cellular DNA.[82](#) Flaxseed oil, containing phytoestrogens, has also been shown to prevent estrogen related tumor cell growth *in vitro* and in mice.[83](#) In addition, a preliminary study found that a combination of phytoestrogens and fibers taken orally could be as effective as COX-2 inhibitors, which block an enzyme important for colorectal cancer. The study concluded that the phytoestrogen/fiber dietary supplement may prevent progression of colorectal cancer in patients with familial adenomatous polyposis.[84](#)

Research supports a role for phytoestrogens in complementary therapy; genistein has been reported to prevent the bone damage that often accompanies chemotherapy.[85](#) One clinical trial, currently recruiting participants, will investigate whether genistein can improve the effectiveness of chemotherapy in colorectal cancer patients.[86](#)

On the other hand, phytoestrogens are also suspected to cause cancer and improper fetal development.[76](#) Some studies have shown that phytoestrogens increase breast cancer cell growth *in vitro*.[78](#) [87](#) Some European countries have even recommended maximum levels of soy intake per day.[76](#)

Currently, researchers are conducting several clinical trials designed to investigate the potential role of phytoestrogens in chemoprevention.[78](#) One phase II trial showed that genistein could decrease activation of EGFR, an important receptor involved in growth of cancer cells, in patients with bladder cancer. The study found no significant differences in other markers.[88](#) Other trials are investigating whether phytoestrogens, via dietary supplementation, can decrease prostate cancer progression.[89](#) [90](#) For information about ongoing clinical trials involving phytoestrogens, please visit our section on [Finding Clinical Trials](#).

Learn more about [angiogenesis](#), [apoptosis](#), [metastasis](#) and [proliferation](#).

## For Further Reading

The National Cancer Institute has published a Physician Data Query (PDQ) [summary](#) on soy and prostate cancer, written specifically for patients.

## US Food and Drug Administration Approval

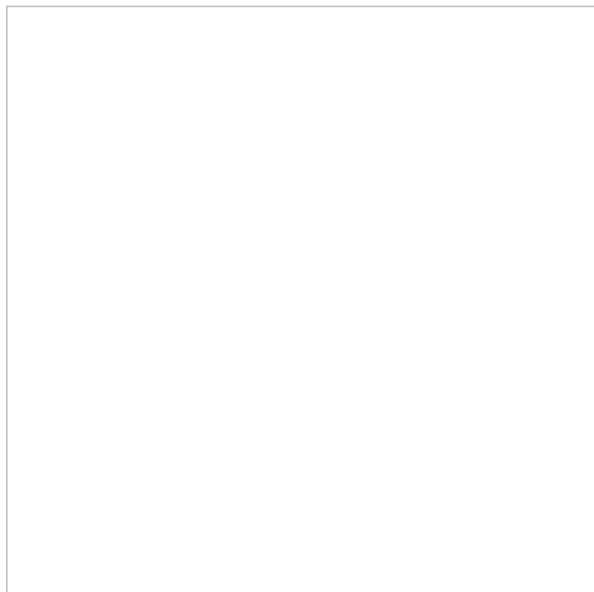
There is not enough evidence that phytoestrogens are effective in the fight against cancer, and they have not been approved by the FDA for cancer treatment.[11](#)

\*It is important to keep in mind that many cancer treatments, including chemotherapy and radiation, work by generating free radicals in order to destroy cancer cells. If a cancer patient takes antioxidants while undergoing radiation or chemotherapy treatment, it is possible that these compounds may protect tumor cells from the desired free radicals. Doctors may recommend that patients undergoing these treatments avoid antioxidants so that the treatment is as effective as possible.[12](#)

Please be sure to see our [notice on complementary therapies](#). To better understand and evaluate the research described above, read our [Introduction to Scientific Research](#).

---

## Pycnogenol



Structure of Pycnogenol

### Classification

Phytochemical, Polyphenol, Flavonoid, Proanthocyanidin

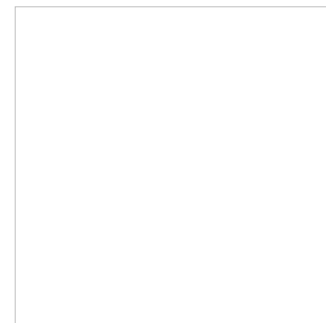
### Intro and Background

Pycnogenol is a product derived from the bark of the French Pine Tree (*Pinus pinaster*). [91](#) Extract from the bark of this tree contains compounds known as flavonoids, procyanidins, and proanthocyanidins that are also found in grapes and cocoa. [92](#) [93](#) This extract is widely used in Europe as a dietary supplement to protect nerve cells, increase sperm activity, increase tissue function, decrease blood pressure, and alleviate asthma symptoms. [94](#) Pycnogenol and other proanthocyanidins are being investigated for their possible antioxidant, anti-inflammatory, and anti-platelet functionality. [92](#) [95](#) [93](#)

### Scientific Research

This natural extract has been recognized for its ability to reduce oxidative damage and prevent some processes that can often lead to cancer. [96](#) It was shown to induce [apoptosis](#) and slow down the reproduction of oral, [97](#) [98](#) leukemia, [99](#) breast, [100](#) , and ovarian [101](#) cancer cells *in vitro*. [102](#) A mixture derived from a related tree, the Taiwan short pine (*Pinus morrisonicola*), has also been shown to kill leukemia cells *in vitro*. [103](#)

Pycnogenol has also been shown to slow the development of skin cancer *in vivo*. [93](#) What's more, even pycnogenol that has been metabolized, or processed by the human body, can cause fibrosarcoma cells to die *ex vivo*. [104](#) Much of the research pertaining to pycnogenol and proanthocyanidins involves their ability to prevent cancer. Yet, one group reported that pycnogenol can treat moderate, but not severe, oral mucositis, a painful side effect of chemotherapy that may get in the way of proper nutrition. [105](#)



French Pine trees

One clinical study, sponsored by the University of Wisconsin and the National Center for Complementary and Integrative Health, investigated whether pycnogenol could benefit breast cancer survivors who suffered from lymphedema, or buildup of fluid in the lymph nodes, a common side-effect of breast cancer treatment. [106](#) For information about ongoing clinical trials involving pycnogenol, please visit our section on [Finding Clinical Trials](#).

### US Food and Drug Administration Approval

There is not enough evidence that pycnogenol is effective in the fight against cancer, and it has not been approved by the FDA for cancer treatment. [11](#)

\*It is important to keep in mind that many cancer treatments, including chemotherapy and radiation, work by generating free radicals in order to destroy cancer cells. If a cancer patient takes antioxidants while undergoing radiation or chemotherapy

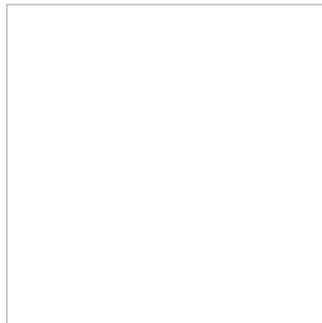
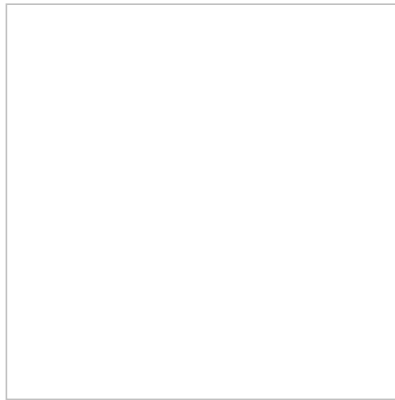
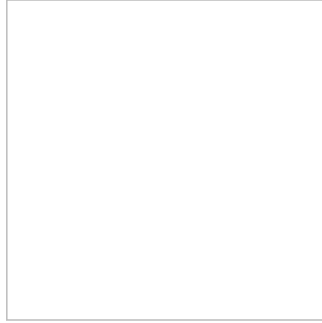
treatment, it is possible that these compounds may protect tumor cells from the desired free radicals. Doctors may recommend that patients undergoing these treatments avoid antioxidants so that the treatment is as effective as possible. [12](#)

---

Please be sure to see our [notice on complementary therapies](#). To better understand and evaluate the research described above, read our [Introduction to Scientific Research](#).

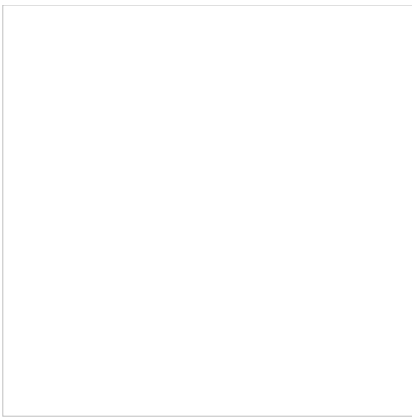
---

## Resveratrol



### Classification

Phytochemical, Polyphenol, Phytoestrogen, Anthocyanin



Structure of Resveratrol

## Intro and Background

Resveratrol is a compound commonly found in the skin and seeds of red grapes. It can also be obtained from berries, nuts, wine, and supplements. [107](#) [108](#) In plants, this compound helps defend against fungal infections. [109](#)

Cancer treatment with resveratrol began in 1925 when Johanna Brandt, a South African dietician, claimed that she was able to cure herself of stomach cancer by eating a grape diet. [110](#) She opened the Harmony and Healing Centre in New York City in 1928 but was quickly charged with practicing medicine without a license. [111](#) [112](#) The American Cancer Society has examined Brandt's grape cure four times and found no therapeutic value for its use. [111](#) Another source of interest regarding resveratrol is the "French paradox": French people typically eat diets high in fat but experience fewer incidences of heart disease. [113](#)

Scientists are researching this compound because of its antioxidant activity [114](#) and because it may interfere with [angiogenesis](#) and [metastasis](#) [115](#) while inducing [apoptosis](#) [116](#) of cancer cells. It is also being studied for potential abilities to prevent cancer, protect endothelial cells, [117](#) and prevent heart disease. [116](#) Resveratrol has not shown adverse side effects in animal trials when supplements have been used. [115](#)

## Scientific Research

Resveratrol has shown that it can induce apoptosis [118](#) in cancerous cells and reduce cancer cell growth [116](#) in *in vitro* studies. Experiments involving mice have also indicated that resveratrol can induce apoptosis in cancer cells. [119](#) Others have shown that resveratrol can inhibit processes like epithelial-mesenchymal transition, oxidative stress, and inflammation, all of which contribute to cancer progression. [120](#) [79](#) Resveratrol also has been shown to regulate the progression of [cancer stem cells](#), hindering them from developing into tumors. *In vitro* experiments, however, show that resveratrol is capable of enhancing the anti-tumor growth effects of the chemotherapy drug rapamycin. These experiments also showed a lowered incidence of cancer resistance to rapamycin, which is likely a consequence of resveratrol suppressing AKT signalling [121](#) .

A study using two breast cancer cell lines demonstrated that the effects of resveratrol were dependent on the amount used. Lower doses stimulated breast cancer cell growth *in vitro* and higher doses blocked growth. [108](#) There is still much to be learned about how resveratrol affects cancer cells and cancer patients.

Some work has been done in people, but because of small patient numbers, differences in study designs, and short treatment times, researchers have not reached a conclusion about the ability of resveratrol (or similar molecules) to treat cancer. [122](#) Despite encouraging results in cells, resveratrol, like curcumin, is poorly absorbed by the body, and high concentrations are necessary for significant results. [120](#) Consequently, though laboratory studies indicate that resveratrol can prevent cancer progression, the results of clinical trials have not been as promising. [120](#) [123](#)

Clinical studies at UC Irvine, The National Cancer Institute, the University of Oslo, the University of Wisconsin, and the University of Michigan are investigating how effectively resveratrol can treat cancer. [124](#) In the UC Irvine trial, resveratrol was able to negatively affect a pathway key to colon cancer development. [125](#) This trial, along with the NCI trial, suggests a role for resveratrol in preventing cancer rather than treating it. [126](#) For information about ongoing clinical trials involving resveratrol, please visit our section on [Finding Clinical Trials](#).

Researchers have also studied the effects of different combinations of nutrients on mouse prostate cancer, both in culture and in a mouse model of prostate cancer. The nutrients with the most effect on prostate cancer cells included: ursolic acid, found in apple peels and rosemary; curcumin; and resveratrol, which is found in red grapes and berries. A lead researcher, Dr. Tiziani, stated, "These nutrients have potential anti-cancer properties and are readily available. We only need to increase concentration beyond levels found in a healthy diet for an effect on prostate cancer cells." [36](#) [127](#)

Learn more about [angiogenesis](#), [apoptosis](#) and [metastasis](#).

## US Food and Drug Administration Approval

There is not enough evidence that resveratrol is effective in the fight against cancer, and it has not been approved by the FDA for cancer treatment. [11](#)

\*It is important to keep in mind that many cancer treatments, including chemotherapy and radiation, work by generating free radicals in order to destroy cancer cells. If a cancer patient takes antioxidants while undergoing radiation or chemotherapy treatment, it is possible that these compounds may protect tumor cells from the desired free radicals. Doctors may recommend that patients undergoing these treatments avoid antioxidants so that the treatment is as effective as possible. [12](#)

---

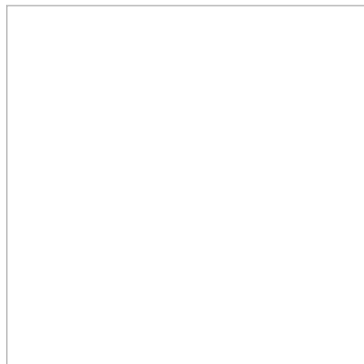
Please be sure to see our [Notice on Complementary Therapies](#). To better understand and evaluate the research described above, read our [Introduction to Scientific Research](#).

---

## Selenium

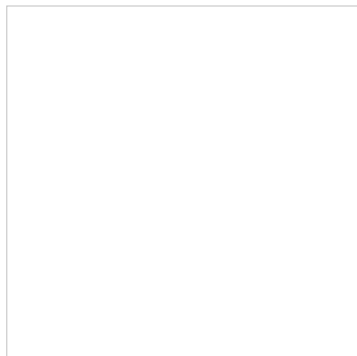
### Often ingested as:

Selenomethionine



Structure of Selenomethionine

### Intro and Background



Selenium is a component of the amino acid selenomethionine, commonly found in soil, forages, and grains. [128](#) This naturally occurring amino acid is essential for proper nutrition and is often obtained from meats, seafood, and plants. [129](#) The amount of selenium in plants, animals, and humans depends on the selenium concentration of the soil where they were raised. Investigators started to look at selenium as an anticancer agent when a report suggested that the average selenium intake was lower among nations that showed an increased risk for cancer. [130](#)

In many studies, selenium is also paired with Vitamin E to investigate their combined cancer fighting abilities. For the most part, research is focused on the ability of selenium to prevent cancer rather than fight it. The exact mechanism by which it works is unknown, but it may fight cancer-causing events in several different ways: it enhances processes that normally fight cancerous cells [131](#) and prevents harmful molecules from binding to and changing DNA. [132](#)

The US Food and Drug administration recommends a daily intake of about 70 µg (with a maximum of 400 µg/day) for adults as part of a normal, healthy diet. [133](#)

### Scientific Research

Selenium may be an effective agent to prevent cancer, but more research is needed before a conclusion can be made. [134](#) [135](#) Some studies suggest that a baseline, or minimum, level of selenium intake provides protection from cancer development. [136](#) Studies also show that men are at a reduced risk for prostate cancer when selenium is part of their diet. [133](#) Treatment of prostate cancer cells with selenium *in vitro* can inhibit tumor growth and induce apoptosis. [128](#) [137](#) Selenium-enriched sugars have been found to exert anti-cancer effects, [138](#) as did a selenium-containing chemical compound called Se,Se<sup>-1</sup>,4-phenylenebis(1,2-ethanediyl) bisisoselenourea, with implications for the treatment of liver cancer. [139](#) An ionic compound of selenium, sodium selenite, has also been shown to help treat lymphedema, or swelling of the lymph nodes often caused by radiation therapy and surgery. [140](#) What's more, methylselenol has been reported to slow down the growth of colon tumors in mice. [141](#)

There are some indications that selenium may increase the risk for type II diabetes. [136](#)



[Phase II](#) clinical trials are investigating selenium's ability to prevent and/or treat cancer. Though some trials are complete, results have not been published. For more information about clinical trials involving selenium, visit the US [database](#). For information about ongoing clinical trials involving homeopathy, please visit our section on [Finding Clinical Trials](#).

### For Further Reading

The National Cancer Institute has published a Physician Data Query (PDQ) [summary on selenium and prostate cancer](#), written specifically for patients.

### US Food and Drug Administration Approval

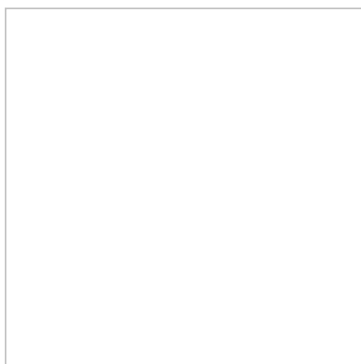
There is not enough evidence that selenium is effective in the treatment of cancer, and it has not been approved by the FDA for cancer treatment. [11](#)

---

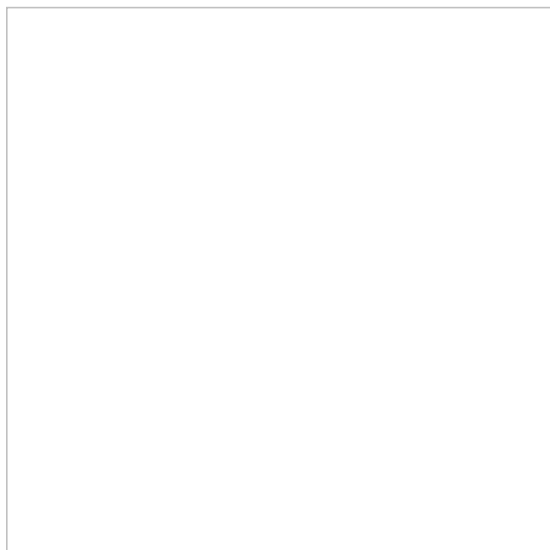
Please be sure to see our [Notice on Complementary Therapies](#). To better understand and evaluate the research described above, read our [Introduction to Scientific Research](#).

---

## Cannabis and Hemp Oil



**Classified as:** Phytochemical, Aromatic Terpenoid



Structure of Cannabis

### Introduction and Background

Cannabis belongs to the Cannabaceae family of plants. These include *Cannabis sativa* (pictured above; Wikimedia), *Cannabis indica*, and *Cannabis ruderalis*.<sup>142</sup> Cannabinoids are chemicals found in Cannabis plants. Cannabinoids bind to receptor proteins on target cells and produce a variety of effects. Cannabinoids can also be produced by animals and are classified based on their origin. Phytocannabinoids are made in plants, other cannabinoids, called endocannabinoids, are found naturally in humans and animals, and synthetic cannabinoids are man-made. Many cannabinoids that are naturally found in plants can now be produced synthetically. The two main cannabinoids found in *Cannabis* are tetrahydrocannabinol (THC), or more specifically,

$\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC), shown in the image above (Wikimedia), and cannabidiol (CBD).[143](#) [144](#) THC is the main psychoactive ingredient. It binds to CB1 and CB2 receptors in the central nervous system and is found in marijuana (from *Cannabis sativa*). THC is thought to be responsible for the euphoria and relaxation felt by marijuana users.[143](#) [144](#) CBD, on the other hand, has low affinity for the CB1 and CB2 receptors and while the way it works is less understood, studies suggest that CBD produces antipsychotic and anxiolytic effects in humans and lessens THC's effects in the body [145](#) . Currently, these cannabinoids and others are being studied for their potential use in the treatment of several different cancers. See more details below.[146](#) [147](#) [148](#) [149](#) [150](#)

## Hemp Oil

Hemp oil is a common (non-scientific) term for extracts made from many different *Cannabis* species. Hemp oil is obtained when hemp seeds are pressed. Hemp oil is legal in the United States. Modern hemp oil manufacturing methods ensure that almost no THC is found in the hemp oil. The seeds used for the oil come from *Cannabis sativa* strains bred to contain only tiny amounts of THC.[151](#)

## Scientific Research

Studies have shown that cannabinoids have a wide variety of effects on cells growing in culture and in animals. The following list is not meant to be complete but gives an overview of the types of effects that have been seen. Some of the results are conflicting, with one study showing benefit and another showing either a lack of benefit or, worse, causing cancer to grow or spread more aggressively.

### Work in cells grown in dishes in the laboratory (also called cell culture or *in vitro*)

1. Manmade (synthetic) chemicals that activate the same receptors as cannabinoids were shown to inhibit the invasive behavior of lung cancer cells and breast cancer cells.[147](#) [148](#)
2. In a system using the major psychoactive cannabinoid found in *C. sativa* ( $\Delta^9$ -THC), research with different breast cancer cells showed that this chemical was NOT able to kill the cells. The use of this natural product actually enhanced the growth of the cancer cells in animals.[149](#)

### Work in animals (also called *in vivo*)

1. Synthetic chemicals that bind to cannabinoid receptors were shown to reduce tumor growth and spread of lung cancer grown in mice. The chemicals seemed to cause the cancer cells to die by blocking the activity of a 'survival' protein, AKT.[147](#)
2. Also in mice, the same chemicals were shown to reduce the growth and spread of breast cancer.[148](#)
3. A study with the natural chemical,  $\Delta^9$ -THC, showed **INCREASED** tumor growth after exposure. The research indicated that the increased tumor growth was due to suppression of the immune system by  $\Delta^9$ -THC.[149](#)

### Work in humans

1. One trial involved the injection of  $\Delta^9$ -THC into the brains of 9 patients with glioblastoma multiforme, a type of brain cancer. The results of the trial indicated that, at least for some patients, the drug reduced the division of the cancer cells *in vitro* and *in vivo*, but the patients did not recover from their disease.[152](#)
2. In another trial, participants were given spray injections of  $\Delta^9$ -THC and cannabidiol for five weeks. The doses were 1-4, 6-10, or 11-16 sprays a day, and a fourth group was given a placebo. The low dose (1-4 sprays) group showed a statistically significant decrease in pain compared to the placebo group.[153](#)

There are indications that the conflicting results seen in some systems are due to different effects caused by different doses of the cannabinoids. This is covered in depth in a 2009 review called "Cannabinoids in the treatment of cancer."[146](#) Several recent reviews of cannabinoids and endocannabinoids in cancer are also available.[154](#) [155](#)

Research published in 2013 shows that the anti-cancer activities of  $\Delta^9$ -THC are, in large part, caused by its effects on a protein called pseudokinase tribbles homologue-3 (TRIB3). TRIB3 is part of a stress response system and when it is present in higher levels, it is able to block the activities of proteins that keep cells alive (including AKT and mTOR).  $\Delta^9$ -THC was shown to increase levels of TRIB3 and cause cancer cell death. It was not able to kill cells missing TRIB3, showing the importance of this protein in the effects of  $\Delta^9$ -THC.[156](#) Because the molecular mechanisms of cannabinoid receptors are still being worked out, further studies on  $\Delta^9$ -THC and other cannabinoids on a variety of cancers are needed.

## **No studies have shown that $\Delta^9$ -THC or other cannabinoids found in marijuana or hemp oil cure any form of cancer**

Cannabinoids are also being studied for other reasons. They can help reduce the effects of cancer and side effects of cancer treatments, like pain, nausea, and loss of appetite (anorexia).[154](#) [157](#) [158](#) [155](#) [159](#) They can also increase the effectiveness of radiation in a type of cancer called glioma.[160](#)

## For Further Reading

The National Cancer Institute has published a Physician Data Query (PDQ) summary about *Cannabis* and cannabinoids. Access the version written for patients [here](#).

[Look for more research studies on cannabinoids and cancer.](#) (opens new window - just type in those words in the search bar)

[View clinical trials involving cannabinoids and cancer.](#)

## US Food and Drug Administration Approval

There is not enough evidence to support cannabinoids as effective in the fight against cancer, and they have not been approved by the FDA for cancer treatment.[58](#) However, some synthetic cannabinoids, called nabilone and dronabinol, are approved to treat the nausea and vomiting associated with chemotherapy.[161](#)

---

Please be sure to see our [notice on complementary therapies](#). To better understand and evaluate the research described above, read our [Introduction to Scientific Research](#).

---

## Essiac<sup>®</sup>, Flor-Essence<sup>®</sup>

### Intro and Background

Essiac<sup>®</sup> is a blend of four herbs: burdock root (*Arctium lappa*), Indian rhubarb (*Rheum palmatum*), sheep sorrel (*Rumex acetosella*) and the inner bark of slippery elm (*Ulmus fulva* or *U. rubra*). [162](#) Flor-Essence<sup>®</sup> contains the previous four herbs as well as red clover (*Trifolium pretense*), blessed thistle (*Carduus benedictus*), kelp (*Laminaria digitata*), and watercress (*Nasturt officinale*). [163](#) The medicine men of the Ojibwa Native American tribe are believed to be the creators of the four herb mixture found in Essiac. [164](#) The treatment became popular in the early 1920s when a Canadian nurse, Rene Caisse, started treating patients with the herbal blend. [165](#) She claimed that Essiac<sup>®</sup> (her last named spelled backwards) improved the quality of life of her patients, prolonged survival, and could even cure cancer. [166](#) The use of these products by cancer patients is largely fueled by anecdotal evidence (a few rare cases) that they can treat or prevent cancer. [167](#) Allegedly, it is also is a remedy for allergies, hypertension, and osteoporosis. [168](#)

### Scientific Research

Essiac<sup>®</sup> has shown to block free radicals and exhibited the ability to protect DNA from damage that can lead to cancer. [169](#) Also, researchers have found that Essiac<sup>®</sup> prevents prostate cancer cells from growing *in vitro*. [164](#) Another study showed that Essiac<sup>®</sup> and Flor-Essence<sup>®</sup> had weak effects on the growth of leukemia and breast cancer cells *in vitro* and only at concentrations higher than would be attained in the body. [165](#) This study also found that the herbal blend increased cancer cell differentiation. Alternatively, another study found that both Essiac<sup>®</sup> and Flor-Essence<sup>®</sup> not only fail to halt tumor enlargement, but can stimulate the growth of breast cancer cells *in vitro*. [167](#) A clinical trial involving Essiac found that it had no effect on quality of life for women with breast cancer. [170](#)

There are currently no active clinical trials investigating Essiac<sup>®</sup> or Flor-Essence<sup>®</sup> and their ability to fight cancer. [171](#) For information about ongoing clinical trials involving Essiac<sup>®</sup> or Flor-Essence<sup>®</sup>, please visit our section on [Finding Clinical Trials](#).

## For Further Reading

The National Cancer Institute has published a Physician Data Query (PDQ) summary on Essiac<sup>®</sup> and Flor-Essence<sup>®</sup>. Access the patient version [here](#).

## US Food and Drug Administration Approval

There is not enough evidence that Essiac<sup>®</sup> and Flor-Essence<sup>®</sup> are effective in the fight against cancer,[172](#) and they have not been approved by the FDA for cancer treatment.[173](#) In fact, Essiac is on the [FDA's list of Fake Cancer "Cures."](#) Essiac<sup>®</sup> and Flor-Essence<sup>®</sup> are available commercially because they're sold as dietary supplements, and dietary supplements do not require FDA approval unless the seller claims that they can cure or prevent disease.[174](#)

---

Please be sure to see our [notice on complementary therapies](#). To better understand and evaluate the research described above, read our [Introduction to Scientific Research](#).

---

## Gerson Therapy

The Gerson Therapy targets chronic diseases like cancer using "an organic, vegetarian diet, raw juices, coffee enemas and natural supplements," according to the company's website. Two clinics are licensed to practice it, one in Hungary and one in

Mexico.[175](#)

However, the FDA has not approved the Gerson therapy, and no preclinical (animal or laboratory) studies examining it are available in the scientific literature. A number of clinical studies (involving humans) are available, most of them as case studies published by Dr. Gerson, but they do not provide conclusive evidence about the regimen.[176](#)

For more information, see the [National Cancer Institute's Physician Data Query \(PDQ\) Cancer Information Summary](#) regarding the Gerson therapy.

---

Please be sure to see our [notice on complementary therapies](#). To better understand and evaluate the research described above, read our [Introduction to Scientific Research](#).

---

## Graviola/Soursop

image of graviola (soursop) plant.

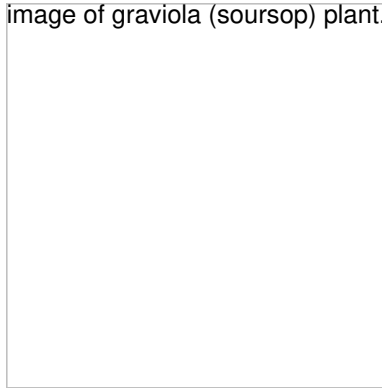


Image obtained from [Wikimedia](#).

### Classification

Phytochemical

### Introduction and Background

Graviola (also known as soursop guyabano, and guanábana) usually refers to the fruit of the tropical tree *Annona muricata*. Sometimes it is referred to as Brazilian paw paw or custard apple - although these are not the same. Extracts from the bark, leaves, roots, and fruits of *Annona muricata* are traditionally used to treat a variety of ailments including bacterial infections, herpesvirus infections, and cancer. However, few scientific studies have tested the medicinal properties of the extracts.[177](#) [178](#)

Graviola leaves contain derivatives of long-chain fatty acids known as annonaceous acetogenins [179](#) [180](#) [178](#), which are believed to exert at least part of their biological effects by inhibiting the production of the cellular energy carrier adenosine triphosphate (ATP).[181](#) [182](#) Because cancer cells require more ATP than normal cells, annonaceous acetogenins are believed to induce the death of cancer cells by starving them of their energy source. The chemicals in graviola have also been shown to inhibit the production (replication) of DNA.[183](#) [184](#)

### Scientific Research

In laboratory studies, graviola extract has been shown to cause impaired function and death of pancreatic cancer cell lines (FG/COL0357 and CD18/HPAF). In immunocompromised mice, oral treatment with graviola extract was shown to reduce the growth and spread of injected pancreatic cancer cells.[182](#) Another study reported that it could prevent pancreatic cancer from advancing to a more dangerous stage by decreasing the ability of cancer cells to multiply.[185](#) According to a more recent *in vitro* study, it can also kill squamous cell carcinoma cells.[186](#)

Graviola fruit extract has also been shown to downregulate the epidermal growth factor receptor (EGFR) oncogene and inhibit breast cancer cell growth in *in vitro* and *in vivo* studies using EGFR-overexpressing human breast cancer cells (MDA-MB-468). The extract, however, did not have an effect on nontumorigenic human breast epithelial cells.[187](#) In an *in vivo* study, 6-7 week old mice were treated with chemicals that can cause (initiate) and accelerate the growth of (promote) skin cancer. Some of the mice also had extracts from *Annona muricata* put on their skin to see if the extract could slow or prevent the growth of skin cancer. The graviola extract was found to suppress tumor initiation and prevent tumor promotion at the highest dosages. No toxic side effects were seen in the mice (in this short study).[188](#)

As for studies in humans, one [Phase 0](#) clinical trial has been completed, in which colorectal cancer patients were given extracts containing graviola, but results are not available.[189](#)

## Side Effects

Although several studies suggest that graviola extracts may have anti-cancer properties, the major bioactive component of the extract, *Annonaceous acetogenins*, may also cause nervous system and/or mental problems. Consumption of the fruit has been linked to nervous system problems, including a form of atypical Parkinson's disease.[190](#) [191](#) [192](#) [193](#) [194](#) In a study in which rats were intravenously given *Annonaceous acetogenins* for 28 days, a decrease in brain ATP levels and abnormalities similar to those found in atypical Parkinson patients were observed.[195](#)

**Several studies suggest that chemicals in graviola (soursop) might be toxic. It should be consumed with caution.**

## US Food and Drug Administration Approval

There is not enough evidence to support the claim that graviola (soursop) is effective in the fight against cancer, and it has not been approved by the FDA for cancer treatment. [11](#)

---

Please be sure to see our [notice on complementary therapies](#). To better understand and evaluate the research described above, read our [Introduction to Scientific Research](#).

---

- [1 a b c](#) Prior RL, Wu X. Anthocyanins: structural characteristics that result in unique metabolic patterns and biological activities. *Free Radic Res.* (2006) 40(10): 1014-28 [[PUBMED](#)]
- [2 a b](#) Zafra-Stone S, YAsmin T., Baqchi M., Chatterjee A., Vinson J.A., Bachi D. Berry anthocyanins as novel antioxidants in human health and disease prevention. *Molecular Nutrition & Food Research.* (2007) 51:6, 675-683 [[PUBMED](#)]
- [3](#) Wu QK, Koponen JM, Mykkanen HM, Torronen AR. Berry phenolic extracts modulate the expression of p21 (WAF1) and Bax but not Bcl-2 in HT-29 colon cancer cells. *J Agric Food Chem.* (2007) 55(4): 1156-63 [[PUBMED](#)]
- [4](#) Valcheva-Kuzmanova S.V., Belcheva A. Colon-available raspberry polyphenols exhibit anti-cancer effects on in vitro models of colon cancer. *Journal of Carcinogenesis* (2007) Apr 18; 6: 4 [[PUBMED](#)]
- [5](#) Ferguson, P. J.; Kurowska, E.; Freeman, D. J.; Chambers, A. F.; Koropatnick, D. J. A flavonoid fraction from cranberry extract inhibits proliferation of human tumor cell lines. *Journal of Nutrition.* 2004, 134, 1529-1535. [[PUBMED](#)]
- [6](#) Seeram, N. P.; Adams, L. S.; Hardy, M. L.; Heber, D. Total cranberry extract versus its phytochemical constituents: antiproliferative and synergistic effects against human tumor cell lines. *Journal of Agric. Food Chem.* 2004, 52, 2512-2517 [[PUBMED](#)]
- [7](#) Anwar S, Fratantonio D, Ferrari D, Saija A, Cimino F, Speciale A. Berry anthocyanins reduce proliferation of human colorectal carcinoma cells by inducing caspase-3 activation and p21 up regulation. *Mol Med Rep.* 2016 Jun 13. [[PUBMED](#)]
- [8](#) Neto CC. Cranberry and blueberry: Evidence for protective effects against cancer and vascular diseases. *Molecular Nutrition & Food Research.* (2007) 51(6): 652-664. [[PUBMED](#)]
- [9](#) Stopper H, Schmitt E, Kobras K. Genotoxicity of phytoestrogens. *Mutat Res.* (2005) 574(1-2):139-55 [[PUBMED](#)]
- [10](#) Neuromed IRCCS. Supplementation With Dietary Anthocyanins and Side Effects of Radiotherapy for Breast Cancer (ATHENA). Apr 2015. [<https://clinicaltrials.gov/ct2/show/NCT02195960?term=NCT02195960&rank=1>]
- [11 a b c d e f g h](#) US Food and Drug Administration website. Accessed 6/20/2016. [<http://www.fda.gov/>]
- [12 a b c d e f g](#) Borek C. Dietary antioxidants and human cancer. *Integr Cancer Ther* (2004). 3: 333-341. [[PUBMED](#)]
- [13 a b c d](#) de Lencastre Novaes LC, Jozala AF, Lopes AM, de Carvalho Santos-Ebinuma V, Mazzola PG, Pessoa Junior A. Stability, purification, and applications of bromelain: A review. [[PUBMED](#)]
- [14 a b](#) Chobotova K, Vernallis AB, Majid FA. Bromelain's activity and potential as an anti-cancer agent: Current evidence and perspectives. *Cancer Lett.* 2010 Apr 28;290(2):148-56. [[PUBMED](#)]
- [15 a b](#) Taussig SJ, Batkin S. Bromelain, the enzyme complex of pineapple (*Ananas comosus*) and its clinical application. An update. *J Ethnopharmacol.* 1988 Feb-Mar;22(2):191-203. [[PUBMED](#)]
- [16 a b](#) Hale LP. Proteolytic activity and immunogenicity of oral bromelain within the gastrointestinal tract of mice. *Int Immunopharmacol.* 2004 Feb;4(2):255-64.
- [17](#) Amini A, Masoumi-Moghaddam S, Ehteda A, Morris DL. Bromelain and N-acetylcysteine inhibit proliferation and survival of gastrointestinal cancer cells in vitro: significance of combination therapy. *J Exp Clin Cancer Res.* 2014 Nov 12;33:92. [[PUBMED](#)]
- [18 a b c](#) Bhatnagar P, Pant AB, Shukla Y, Chaudhari B, Kumar P, Gupta KC. Bromelain nanoparticles protect against 7,12-dimethylbenz[a]anthracene induced skin carcinogenesis in mouse model. *Eur J Pharm Biopharm.* 2015 Apr;91:35-46. [[PUBMED](#)]
- [19](#) Bromelain, Comosain as a New Drug for Treating and Preventing Various Types of Cancer in the Humans. [<https://clinicaltrials.gov/ct2/show/NCT02340845?term=bromelain&rank=2>]
- [20](#) Complementary Therapies for the Reduction of Side Effects During Chemotherapy for Breast Cancer [<https://clinicaltrials.gov/ct2/show/NCT00160901?term=bromelain&rank=5>]
- [21](#) US Food and Drug Administration website. Accessed 3 June 2016. [<http://www.fda.gov/>]
- [22](#) Duvoix A. et al. Chemopreventive and therapeutic effects of curcumin. *Cancer Letters* 223 (2005): 181-190 [[PUBMED](#)]
- [23 a b c d](#) Araujo CAC, Leon LL. Biological activities of *Curcuma longa* L. *Mem Inst Oswaldo Cruz.* (2001) 96(5): 723-728 [[PUBMED](#)]



- [24](#)Garcia-Alloza M, Borrelli LA, Rozkalne A, Hyman BT, Bacskai BJ. Curcumin labels amyloid pathology in vivo, disrupts existing plaques, and partially restores distorted neurites in an Alzheimer mouse model. *J Neurochem.* (2007) Apr 30 [[PUBMED](#)]
- [25](#)Aggarwal S, Ichikawa H, Takada Y, Sandur SK, Shishodia S, Aggarwal BB. Curcumin (diferuloylmethane) down-regulates expression of cell proliferation and antiapoptotic and metastatic gene products through suppression of I $\kappa$ B kinase and Akt activation. *Mol Pharmacol.* (2006) 69(1): 195-206 [[PUBMED](#)]
- [26](#) [a](#) [b](#) [c](#) [d](#) [e](#) Mirzaei H, Naseri G, Rezaee R, Mohammadi M, Banikazemi Z, Reza Mirzaei H, Salehi H, Peyvandi M, Pawelek JM, Sahebkar A. Curcumin: A new candidate for melanoma therapy? *Int J Cancer.* 2016 Jun 9. [[PUBMED](#)]
- [27](#)T. Devasenam K.N. Rajasekaran, G. Gunasekaran, P. Viswwanathan, V.P. Menon, Anti Carcinogenic effect of bis-1,7-(2-hydroxyphenyl)-hepta-1,6-diene-3,5-dione a curcumin analog on DMH-induced colon cancer model. *Pharmacol. Res.* 27 (2003) 133-140 [[PUBMED](#)]
- [28](#)Lin Y.G., Kunnumakkara A., et al. Curcumin Inhibits Tumor Growth and Angiogenesis in Ovarian Carcinoma by targeting the Nuclear Factor- $\kappa$ B Pathway. *Clin Cancer Res* 2007 13: 3423-3430 [[PUBMED](#)]
- [29](#)E. Tourkina, P. Gooz, J.C. Oats, A. Ludwicka-Bradley, R.M. Silver, S. Hoffman, Curcumin-induced apoptosis in scleroderma lung fibroblasts: role of protein kinase cepsilon. *American Journal of respiratory Cellular Molecular Biology* 31(2004): 28-35 [[PUBMED](#)]
- [30](#) [a](#) [b](#) Shindikar A, Singh A, Nobre M, Kirolikar S. Curcumin and Resveratrol as Promising Natural Remedies with Nanomedicine Approach for the Effective Treatment of Triple Negative Breast Cancer. *J Oncol.* 2016;2016:9750785. [[PUBMED](#)]
- [31](#)Zhang Z, Chen H, Xu C, Song L, Huang L, Lai Y, Wang Y, Chen H, Gu D, Ren L, Yao Q. Curcumin inhibits tumor epithelial $\rightarrow$ mesenchymal transition by downregulating the Wnt signaling pathway and upregulating NKD2 expression in colon cancer cells. *Oncol Rep.* 2016 May;35(5):2615-23. [[PUBMED](#)]
- [32](#) [a](#) [b](#) Khan S, Karmokar A, Howells L, Thomas AL, Bayliss R, Gescher A, Brown K. Targeting cancer stem-like cells using dietary-derived agents - Where are we now? *Mol Nutr Food Res.* 2016 Jun;60(6):1295-309. [[PUBMED](#)]
- [33](#)Cao L, Xiao X, Lei J, Duan W, Ma Q, Li W. Curcumin inhibits hypoxia-induced epithelial-mesenchymal transition in pancreatic cancer cells via suppression of the hedgehog signaling pathway. *Oncol Rep.* 2016 Jun;35(6):3728-34. [[PUBMED](#)]
- [34](#)Monisha J, Padmavathi G, Roy NK, Deka A, Bordoloi D, Anip A, Kunnumakkara AB. NF- $\kappa$ B Blockers Gifted by Mother Nature: Prospectives in Cancer Cell Chemosensitization. *Curr Pharm Des.* 2016 Jun 9. [[PUBMED](#)]
- [35](#)Verma V. Relationship and interactions of curcumin with radiation therapy. *World J Clin Oncol.* 2016 Jun 10;7(3):275-83. [[PUBMED](#)]
- [36](#) [a](#) [b](#) Starving Prostate Cancer With What You Eat for Dinner. *UT News.* 2017 Jun 6. [[UT NEWS](#)]
- [37](#)Lodi A, Saha A., Lu X., Wang B., Sentandreu E., Collins M., Kolonin M., DiGiovanni J., Tiziani S., Combinatorial treatment with natural compounds in prostate cancer inhibits prostate tumor growth and leads to key modulations of cancer cell metabolism. 2017. Nature Publishing Group: Precision Oncology. 1(18) Published online June 5, 2017 [[ARTICLE](#)]
- [38](#)Datta S, Misra SK, Saha ML, Lahiri N, Louie J, Pan D, Stang PJ. Orthogonal self-assembly of an organoplatinum(II) metallacycle and cucurbit[8]uril that delivers curcumin to cancer cells. *Proc Natl Acad Sci U S A.* 2018 Aug 7;115(32):8087-8092. doi: 10.1073/pnas.1803800115. PubMed [[PUBMED](#)]
- [39](#)National Library of Medicine. (2016). ClinicalTrials.gov Retrieved June 21, 2016 from the National Institutes of Health Web Site: <http://www.clinicaltrials.gov/ct/search.jsessionid=C04DF10415809DE91678716AA35115A4?term=curcumin%2C+cancer&submit=Search>
- [40](#) [a](#) [b](#) Kanai M, Yoshimura K, Asada M, Imaizumi A, Suzuki C, Matsumoto S, Nishimura T, Mori Y, Masui T, Kawaguchi Y, Yanagihara K, Yazumi S, Chiba T, Guha S, Aggarwal BB. A phase I/II study of gemcitabine-based chemotherapy plus curcumin for patients with gemcitabine-resistant pancreatic cancer. *Cancer Chemother Pharmacol.* 2011 Jul;68(1):157-64. [[PUBMED](#)]
- [41](#)Ryan, Julie. Curcumin for the Prevention of Radiation-induced Dermatitis in Breast Cancer Patients. University of Rochester. June 2012. Clinicaltrials.gov [NCT01042938]. [<https://clinicaltrials.gov/ct2/show/results/NCT01042938?sect=Xa9870156&term=curcumin+cancer&rank=3#outcome4>]
- [42](#)Ryan JL, Heckler CE, Ling M, Katz A, Williams JP, Pentland AP, Morrow GR. Curcumin for radiation dermatitis: a randomized, double-blind, placebo-controlled clinical trial of thirty breast cancer patients. *Radiat Res.* 2013 Jul;180(1):34-43. [[PUBMED](#)]
- [43](#)Ryan, Julie. Oral Curcumin for Radiation Dermatitis. University of Rochester. Feb 2016. clinicaltrials.gov[NCT01246973]. [<https://clinicaltrials.gov/ct2/show/results/NCT01246973?term=curcumin+cancer&rank=35&sect=X01256#all>]
- [44](#) [a](#) [b](#) Polymeric nanoparticle-encapsulated curcumin (nanocurcumin): a novel strategy for human cancer therapy. *Journal of Nanobiotechnology.* (2007) 5: 3 [[PUBMED](#)]
- [45](#) [a](#) [b](#) [c](#) Cabrera C, Artacho R, Gimenez R. Beneficial effects of green tea--a review. *J Am Coll Nutr.* (2006) 2: 79-99 [[PUBMED](#)]
- [46](#)Crespy V, Williamson G. A review of the health effects of green tea catechins in in vivo animal models. *Journal of Nutrition* (2004). 134: 3431-3440. [[PUBMED](#)]
- [47](#)Moyers SB, Kumar NB. Green tea polyphenols and cancer chemoprevention: multiple mechanisms and endpoints for phase II trials. *Nutrition Reviews* (2004). 62: 204-211 [[PUBMED](#)]
- [48](#)Yang Cs, Landau JM, Huang MT, Newmark HL. Inhibition of carcinogenesis by dietary polyphenolic compounds. *Annual Review of Nutrition* (2001). 21: 381-406. [[PUBMED](#)]

- [49](#)Paul B, Hayes CS, Kim A, Athar M, Gilmour SK. Elevated polyamines lead to selective induction of apoptosis and inhibition of tumorigenesis by (-)-epigallocatechin-3-gallate (EGCG) in ODC/Ras transgenic mice. *Carcinogenesis* (2005). 26: 119-124. [[PUBMED](#)]
- [50](#)Jung YD, Kim MS, Shin BA, Chay KO, Ahn BW, Liu W, Bucana CD, Gallick GE, Ellis LM. EGCG, a major component of green tea, inhibits tumour growth by inhibiting VEGF induction in human colon carcinoma cells. *British Journal of Cancer*. (2001) 84(6):844-50 [[PUBMED](#)]
- [51 a b c d e](#) Peter B, Bosze S, Horvath R. Biophysical characteristics of proteins and living cells exposed to the green tea polyphenol epigallocatechin-3-gallate (EGCG): review of recent advances from molecular mechanisms to nanomedicine and clinical trials. *Eur Biophys J*. 2016 Jun 16. [[PUBMED](#)]
- [52](#)Zhu BH, Zhan WH, Li ZR, Wang Z, He YL, Peng JS, Cai SR, Ma JP, Zhang CH. Epigallocatechin-3-gallate inhibits growth of gastric cancer by reducing VEGF production and angiogenesis. *World Journal of Gastroenterology*. (2007) 13(8): 1162-9. [[PUBMED](#)]
- [53](#)Henning SM, Wang P, Said JW, Huang M, Grogan T, Elashoff D, Carpenter CL, Heber D, Aronson WJ. Randomized clinical trial of brewed green and black tea in men with prostate cancer prior to prostatectomy. *Prostate*. 2015 Apr 1;75(5):550-9. [[PUBMED](#)]
- [54](#)McLarty, Jerry. A Study of the Effect of Polyphenon E (Green Tea Extract) on Breast Cancer Progression. Sep 2012. Louisiana State University Health Sciences Center Shreveport. [ClinicalTrials.gov](http://ClinicalTrials.gov)[NCT00676793]. [<https://clinicaltrials.gov/ct2/show/NCT00676793?sect=X870156&term=green+tea+cancer&rank=26#outcome2>]
- [55](#)McLarty, Jerry. Green Tea Extract and Prostate Cancer. June 2012. Louisiana State University Health Sciences Center Shreveport. [ClinicalTrials.gov](http://ClinicalTrials.gov)[NCT00676780]. [<https://clinicaltrials.gov/ct2/show/NCT00676780?sect=X980156&term=green+tea+cancer&rank=21#outcome3>]
- [56](#)National Cancer Institute (NCI). Green Tea Extract in Treating Patients With Nonmetastatic Bladder Cancer. Mar 2016. [ClinicalTrials.gov](http://ClinicalTrials.gov) [NCT00666562]. [<https://clinicaltrials.gov/ct2/show/NCT00666562?sect=Xic970156&term=green+tea+cancer&rank=16#outcome12>]
- [57](#)Weronica E. Ek, Elmar W. Tobi, Muhammad Ahsan, Erik Lampa, Erica Ponz, i Soterios A. Kyrtopoulos, Panagiotis Georgiadis, L.H. Lumey, Bastiaan T. Heijmans, Maria Botsivali Ingvar A. Bergdahl, Torgny Karlsson, Mathias Rask-Andersen, Domenico Palli, Erik Ingelsson, Åsa K. Hedman, Lena M. Nilsson, Paolo Vineis, Lars Lind, James M. Flanagan, Åsa Johansson, on behalf of the Epigenome-Wide Association Study Consortium, Tea and coffee consumption in relation to DNA methylation in four European cohorts. (2017) *Human Molecular Genetics*, Volume 26, Issue 16, 15, Pages 3221–3231 [[DOI:10.1093/hmg/ddx194](https://doi.org/10.1093/hmg/ddx194)]
- [58 a b](#) US Food and Drug Administration website. Accessed 6/20/2016. [<http://www.fda.gov/>]
- [59](#)Mueller LA, et al, (2005) The tomato sequencing project, the first cornerstone of the international solanaceae project (SOL). In: *ENCYCLOPEDIA OF LIFE SCIENCES*. John Wiley & Sons, Ltd: Chichester [<http://www3.interscience.wiley.com/cgi-bin/fulltext/110473756/PDFSTART>]
- [60](#)Stacewicz-Sapuntzakis M, Bowen PE. Role of lycopene and tomato products in prostate health. *Biochim Biophys Acta*. (2005) 1740(2): 202-5. Review [[PUBMED](#)]
- [61 a b](#) Ellinger S, Ellinger J, Stehle P. Tomatoes, tomato products and lycopene in the prevention and treatment of prostate cancer: do we have the evidence from intervention studies? *Curr Opin Clin Nutr Metab Care*. (2006) 9(6): 722-7. [[PUBMED](#)]
- [62](#)Ramos-Bueno RP, Romero-González R, González-Fernández MJ, Guil-Guerrero JL. Phytochemical composition and in vitro antitumor activities of selected tomato varieties. *J Sci Food Agric*. 2016 Apr 7. [[PUBMED](#)]
- [63](#)E. Kotake-Nara, M. Kushiro, H. Zhang, T. Sugawara, K. Miyashita, A. Nagao, Carotenoids affect proliferation of human prostate cancer cells. *J. Nutr*. 131 (2001) 3303-3306 [[PUBMED](#)]
- [64](#)Yang CM, Yen YT, Huang CS, Hu ML. Growth inhibitory efficacy of lycopene and  $\beta$ -carotene against androgen-independent prostate tumor cells xenografted in nude mice. *Mol Nutr Food Res*. 2011 Apr;55(4):606-12. [[PUBMED](#)]
- [65 a b](#) Gong X, Marisiddaiah R, Zaripheh S, Wiener D, Rubin LP. Mitochondrial Beta-Carotene 9, 10 Oxygenase Modulates Prostate Cancer Growth via NF-kappaB Inhibition: a Lycopene-Independent Function. *Mol Cancer Res*. 2016 Jul 12. [[PUBMED](#)]
- [66](#)National Institutes of Health. Hormone Therapy for Prostate Cancer. 2014. [[NCI](#)]
- [67](#)T.W.-M. Boileau, Z. Liao, S. Kim, S. Lemeshow, J.W. Erdman Jr., S.K. Clinton. Prostate carcinogenesis in N-methyl-N-nitrosourea(NMU)-testosterone-treated rats fed tomato powder, lycopene or energy-restricted diets. *Journal Natl. Cancer Inst*. 95 (2003) 1578-1586 [[PUBMED](#)]
- [68](#)Gann PH, Deaton RJ, Rueter EE, van Breemen RB, Nonn L, Macias V, Han M, Ananthanarayanan V. A Phase II Randomized Trial of Lycopene-Rich Tomato Extract Among Men with High-Grade Prostatic Intraepithelial Neoplasia. *Nutr Cancer*. 2015;67(7):1104-12. [[PUBMED](#)]
- [69](#)Brown, Powel H. Lycopene in Treating Patients Undergoing Radical Prostatectomy for Prostate Cancer. 2013. University of Texas MD Anderson Phase I/II Prevention Consortium and National Cancer Institute. [[NCT00450749](https://clinicaltrials.gov/ct2/show/NCT00450749)]
- [70](#)Schwartz, Steven. Tangerine or Red Tomato Juice in Treating Patients With Prostate Cancer Undergoing Surgery. 2015. Ohio State University Comprehensive Cancer Center, Riverside Methodist Hospital. [[NCT02144649](https://clinicaltrials.gov/ct2/show/NCT02144649)]
- [71 a b c d](#) Thompson LU, Boucher BA, Liu Z, Cotterchio M, Kreiger N. Phytoestrogen content of foods consumed in Canada, including isoflavones, lignans, and coumestrol. *Nutr Cancer*. (2006) 54(2):184-201 [[PUBMED](#)]
- [72 a b](#) Yano S, Umeda D, Yamashita T, Ninomiya Y, Sumida M, Fujimura Y, Yamada K, Tachibana H. Dietary flavones suppresses IgE and Th2 cytokines in OVA-immunized BALB/c mice. *Eur J Nutr*. (2007) May 11 [[PUBMED](#)]
- [73](#)Horn-Ross PL, Barnes S, Lee M, Coward L, Mandel JE, Koo J, John EM, Smith M. Assessing phytoestrogen exposure

in epidemiologic studies: development of a database (United States). *Cancer Causes Control*. (2000) 11(4):289-98 [PUBMED]

- [74 a b](#) Cotterchio M, Boucher BA, Manno M, Gallinger S, Okey A, Harper P. Dietary phytoestrogen intake is associated with reduced colorectal cancer risk. *J Nutr*. (2006) 136(12): 3046-53. [PUBMED]
- [75](#) Kurzer MS, Xu X. Dietary Phytoestrogens. *Annual Review of Nutrition* (1997) 17:359-81 [PUBMED]
- [76 a b c](#) Sitori CR, Arnold A, Johnson SK. Phytoestrogens: End of Tale? *Ann Med*. 2005; 37(6): 423-38 [PUBMED]
- [77](#) Markiewicz L, Garey J, Adlercreutz H, Gurbide E. In Vitro Bioassay of Non-Steroidal Phytoestrogens. *Journal of Steroid Biochemistry Molecular Biology* (1993) 45(5): 299-405 [PUBMED]
- [78 a b c](#) Tempfer CB, Bentz EK, Leodolter S, Tscherne G, Reuss F, Cross HS, Huber JC. Phytoestrogens in clinical practice: a review of the literature. *Fertil Steril*. (2007) 87(6): 1243-9 [PUBMED]
- [79 a b](#) Lee GA, Hwang KA, Choi KC. Roles of Dietary Phytoestrogens on the Regulation of Epithelial-Mesenchymal Transition in Diverse Cancer Metastasis. *Toxins (Basel)*. 2016 May 24;8(6). [PUBMED]
- [80](#) Chen YC, Nagpal ML, Stocco DM, Lin T. Effects of Genistein, Resveratrol, and Quercetin on Steroidogenesis and Proliferation of MA-10 mouse Leydig Tumor Cells. *Journal of Endocrinology*. (2007) 192 (3); 527-37 [PUBMED]
- [81](#) Kang NH, Shin HC, Oh S, Lee KH, Lee YB, Choi KC. Soy milk digestion extract inhibits progression of prostate cancer cell growth via regulation of prostate cancer-specific antigen and cell cycle-regulatory genes in human LNCaP cancer cells. *Mol Med Rep*. 2016 Jun 17. [PUBMED]
- [82](#) Zafar A, Singh S, Naseem I. Cu(II)-coumestrol interaction leads to ROS-mediated DNA damage and cell death: a putative mechanism for anticancer activity. *J Nutr Biochem*. 2016 Jul;33:15-27. [PUBMED]
- [83](#) Bergman Jungstrom M, Thompson LU, Dabrosin C. Flaxseed and its lignans inhibit estradiol-induced growth, angiogenesis, and secretion of vascular endothelial growth factor in human breast cancer xenografts in vivo. *Clin Cancer Res*. (2007) 13(3):1061-7. [PUBMED]
- [84](#) Calabrese C, Rizzello F, Gionchetti P, Calafiore A, Pagano N, De Fazio L, Valerii MC, Cavazza E, Strillacci A, Comelli MC, Poggioli G, Campieri M, Spisni E. Can supplementation of phytoestrogens/insoluble fibers help the management of duodenal polyps in familial adenomatous polyposis? *Carcinogenesis*. 2016 Jun;37(6):600-6. [PUBMED]
- [85](#) King TJ, Shandala T, Lee AM, Foster BK, Chen KM, Howe PR, Xian CJ. Potential Effects of Phytoestrogen Genistein in Modulating Acute Methotrexate Chemotherapy-Induced Osteoclastogenesis and Bone Damage in Rats. *Int J Mol Sci*. 2015 Aug 6;16(8):18293-311. [PUBMED]
- [86](#) Holcombe, Randall F. Genistein in Treatment of Metastatic Colorectal Cancer. 2016. Icahn School of Medicine at Mount Sinai, DSM Nutritional Products, Inc. <https://clinicaltrials.gov/ct2/show/NCT01985763?term=phytoestrogens+cancer&rank=7>
- [87](#) Rice S. Whitehead SA. Phytoestrogens and Breast Cancer- Promoters or Protectors? *Endocrin- Related Cancer*. (2006) 13(4): 995-1015 [PUBMED]
- [88](#) National Cancer Institute. Phase II Study of Isoflavone G-2535 (Genistein) in Patients With Bladder Cancer. 2016. [Clinicaltrials.gov\[NCT00118040\]. \[https://clinicaltrials.gov/ct2/show/NCT00118040?term=phytoestrogens+cancer&rank=14\]](https://clinicaltrials.gov/ct2/show/NCT00118040?term=phytoestrogens+cancer&rank=14)
- [89](#) Hedelin, Maria. Can Dietary Phytoestrogens Slow Down Prostate Tumor Proliferation? (PRODICA). 2016. Sahlgrenska University Hospital, Goteborg University. [Clinicaltrials.gov\[NCT02759380\]. \[https://clinicaltrials.gov/ct2/show/NCT02759380?term=phytoestrogens+cancer&rank=1\]](https://clinicaltrials.gov/ct2/show/NCT02759380?term=phytoestrogens+cancer&rank=1)
- [90](#) Vodovotz, Yael. Soy Isoflavones in Treating Patients With Recurrent Prostate Cancer or Rising Prostate-Specific Antigen. Ohio State University Comprehensive Cancer Center, National Cancer Institute. 2015. [Clinicaltrials.gov\[NCT01682941\]. \[https://clinicaltrials.gov/ct2/show/NCT01682941?term=phytoestrogens+cancer&rank=3\]](https://clinicaltrials.gov/ct2/show/NCT01682941?term=phytoestrogens+cancer&rank=3)
- [91](#) Huang WW, Yang JS, Lin, CF, HO WJ, Lee MR. Pycnogenol induces differentiation and apoptosis in human promyeloid leukemia HL-60 cells. *Leuk Res*. (2005) 6: 685-92. [PUBMED]
- [92 a b](#) Golanski J, Muchova J, Golanski R, Durackova Z, Markuszewski L, Watala C. Does pycnogenol intensify the efficacy of acetylsalicylic acid in the inhibition of platelet function? In vitro experience. *Postepy Hig Med Dosw (Online)*. (2006) 60: 316-21. [PUBMED]
- [93 a b c](#) Sime S, Reeve VE. Protection from inflammation, immunosuppression and carcinogenesis induced by UV radiation in mice by topical Pycnogenol. *Photochem Photobiol*. (2004) 79(2): 193-8 [PUBMED]
- [94](#) Huang WW, Yang JS, Lin, CF, HO WJ, Lee MR. Pycnogenol induces differentiation and apoptosis in human promyeloid leukemia HL-60 cells. *Leuk Res*. (2005) 6: 685-92. [PUBMED]
- [95](#) Baliga MS, Katiyar SK. Chemoprevention of photocarcinogenesis by selected dietary botanicals. *Photochem Photobiol Sci*. 2006 Feb;5(2):243-53. Epub 2005 Aug 12. [PUBMED]
- [96](#) Peng Q, Wei Z, Lau BH. Pycnogenol inhibits tumor necrosis factor-alpha-induced nuclear factor kappa B activation and adhesion molecule expression in human vascular endothelial cells. *Cell Mol Life Sci*. (2000) 57(5): 834-41. [PUBMED]
- [97](#) Yang IH, Shin JA, Kim LH, Kwon KH, Cho SD. The caspase 3-dependent apoptotic effect of pycnogenol in human oral squamous cell carcinoma HSC-3 cells. *J Clin Biochem Nutr*. 2016 Jan;58(1):40-7. [PUBMED]
- [98](#) Yang IH, Shin JA, Cho SD. Pycnogenol Induces Nuclear Translocation of Apoptosis-inducing Factor and Caspase-independent Apoptosis in MC-3 Human Mucoepidermoid Carcinoma Cell Line. *J Cancer Prev*. 2014 Dec;19(4):265-72. [PUBMED]
- [99](#) *Leuk Res*. (2005) 6: 685-92. [PUBMED]
- [100](#) H.T. Huynh and R.W. Teel. Selective induction of apoptosis in human mammary cancer cells (MCF-7) by Pycnogenol. *Anticancer Res* (2000) 20: 24172420 [PUBMED]
- [101](#) BuzZard AR, Lau BHS. Pycnogenol reduces talc-induced neoplastic transformation in human cell cultures. *Phytother Res*. 2007 Jun;21(6):579-86. [PUBMED]



- [102](#)Pycnogenol induces differentiation and apoptosis
- [103](#)Hsu TY, Sheu SC, Liaw ET, Wang TC, Lin CC. Anti-oxidant activity and effect of Pinus morrissonicola Hay. on the survival of leukemia cell line U937. *Phytomedicine*. (2005) 12(9): 663-9 [\[PUBMED\]](#)
- [104](#)Harati K, Slodnik P, Chromik AM, Behr B, Goertz O, Hirsch T, Kapalschinski N, Klein-Hitpass L, Kolbenschlager J, Uhl W, Lehnhardt M, Daigeler A. Proapoptotic effects of pycnogenol on HT1080 human fibrosarcoma cells. *Int J Oncol*. 2015 Apr;46(4):1629-36. [\[PUBMED\]](#)
- [105](#)Khurana H, Pandey RK, Saksena AK, An evaluation of Vitamin E and Pycnogenol in children suffering from oral mucositis during cancer chemotherapy. *Oral Dis*. 2013 Jul;19(5):456-64. [\[PUBMED\]](#)
- [106](#)Hutson, Paul R. Pycnogenol for the Treatment of Lymphedema. University of Wisconsin, Madison and National Center for Complementary and Integrative Health. April 2008. [\[NCT00214032\]](#)
- [107](#)Alkhalaf M. Resveratrol-induced growth inhibition in MDA-MB-231 breast cancer cells is associated with mitogen-activated protein kinase signaling and protein translation. *Eur J Cancer Prev*. (2007)16(4):334-41 [\[PUBMED\]](#)
- [108 a b](#) Basly JP, Marre-Fournier F, Le Bail JC, Habrioux G, Chulia J. Estrogenic/antiestrogenic and scavenging properties of (E)- and (Z)-resveratrol. *Life Sci*. (2000) 66(9): 769-77. [\[PUBMED\]](#)
- [109](#)Alkhalaf M. Resveratrol-induced growth inhibition in MDA-MB-231 breast cancer cells is associated with mitogen-activated protein kinase signaling and protein translation. *Eur J Cancer Prev*. (2007)16(4):334-41 [\[PUBMED\]](#)
- [110](#)Brandt, Johanna. How to Conquer Cancer, Naturally (The Grape Cure). 2nd edition. Tree of Life Publications, 1996
- [111 a b](#) Barrett S. The Grape Cure. (2001). Accessed 2 June 2010 [\[http://www.quackwatch.org/01QuackeryRelatedTopics/Cancer/grape.html\]](http://www.quackwatch.org/01QuackeryRelatedTopics/Cancer/grape.html)
- [112](#)Cease and Desist Orders. Abstracts of Certain Federal Trade Commission Releases. Grape Cure for Cancer. *JAMA* 116:2525, 1941 File accessed 6/1/2010 [\[http://jama.ama-assn.org/content/vol116/issue22/index.dtl\]](http://jama.ama-assn.org/content/vol116/issue22/index.dtl)
- [113](#)Opie LH, Lecour S. The red wine hypothesis: from concepts to protective signaling molecules. *Eur Heart J*. (2007) 7 [\[PUBMED\]](#)
- [114](#)de Almeida LM, Pineiro CC, et al, "Pritective effects of resveratrol on hydrogen peroxide induced toxicity in primary cortical astrocyte cultures." *Neurochem Res*. (2007) Jun 27. [\[PUBMED\]](#)
- [115 a b](#) Delmas D, Lancon A, Colin D, Jannin B, Latruffe N. Resveratrol as a chemopreventative agent: a promising molecule for fighting cancer. *Curr Drug Targets*. (2006) 7(4): 423-42. [\[PUBMED\]](#)
- [116 a b c](#) Alkhalaf M. Resveratrol-induced growth inhibition in MDA-MB-231 breast cancer cells is associated with mitogen-activated protein kinase signaling and protein translation. *Eur J Cancer Prev*. (2007)16(4):334-41 [\[PUBMED\]](#)
- [117](#)Chow SE, Hshu YC, Wand JS, Chen JK. Resveratrol attenuates oxLDL-stimulated NADPH oxidase activity and protects endothelial cells from oxidative functional damage. *J Appl Physiol*. (2007) 102(4): 1520-7 [\[PUBMED\]](#)
- [118](#)Ahmad, Kashif A, et al. Protein kinase CK2 modulates apoptosis induced by resveratrol and epigallocatechin-3-gallate in prostate cancer cells. *Molecular Cancer Therapeutics* 6.3 (2007): 1006-12 [\[PUBMED\]](#)
- [119](#)Fulda S. and Debatin, KM. Resveratrol modulation of signal transduction in apoptosis and cell survival. *Cancer Detection and Prevention* (2006) 30:3, 217-223 [\[PUBMED\]](#)
- [120 a b c](#) Shindikar A1, Singh A1, Nobre M1, Kirolikar S. Curcumin and Resveratrol as Promising Natural Remedies with Nanomedicine Approach for the Effective Treatment of Triple Negative Breast Cancer. *J Oncol*. 2016;2016:9750785. [\[PUBMED\]](#)
- [121](#)"Resveratrol enhances the anti-tumor activity of the mTOR inhibitor rapamycin in multiple breast cancer cell lines mainly by suppressing rapamycin-induced AKT signalling." [\[http://www.ncbi.nlm.nih.gov/pubmed/21168265\]](http://www.ncbi.nlm.nih.gov/pubmed/21168265)
- [122](#)Von Low E.C, Perabo F.G., Siesner N., Muller S.C. Review. Facts and fiction of phytotherapy for prostate cancer: a critical assessment of preclinical and clinical data. *In Vivo*. (2007) 21:2, 189-204. [\[PUBMED\]](#)
- [123](#)Maru GB, Hudlikar RR, Kumar G, Gandhi K, Mahimkar MB. Understanding the molecular mechanisms of cancer prevention by dietary phytochemicals: From experimental models to clinical trials. *World J Biol Chem*. 2016 Feb 26;7(1):88-99.[\[PUBMED\]](#)
- [124](#)National Library of Medicine. National Institutes of Health. [Clinicaltrials.gov](http://clinicaltrials.gov). Retrieved August 2016.
- [125](#)Nguyen AV, Martinez M, Stamos MJ, Moyer MP, Planutis K, Hope C, Holcombe RF. Results of a phase I pilot clinical trial examining the effect of plant-derived resveratrol and grape powder on Wnt pathway target gene expression in colonic mucosa and colon cancer. *Cancer Manag Res*. 2009 Apr 3;1:25-37.[\[PUBMED\]](#)
- [126](#)Brown VA, Patel KR, Viskaduraki M, Crowell JA, Perloff M, Booth TD, Vasilinin G, Sen A, Schinas AM, Piccirilli G, Brown K, Steward WP, Gescher AJ, Brenner DE. Repeat dose study of the cancer chemopreventive agent resveratrol in healthy volunteers: safety, pharmacokinetics, and effect on the insulin-like growth factor axis. *Cancer Res*. 2010 Nov 15;70(22):9003-11.[\[PUBMED\]](#)
- [127](#)Lodi A, Saha A., Lu X., Wang B., Sentandreu E., Collins M., Kolonin M., DiGiovanni J., Tiziani S., Combinatorial treatment with natural compounds in prostate cancer inhibits prostate tumor growth and leads to key modulations of cancer cell metabolism. 2017. Nature Publishing Group: Precision Oncology. 1(18) Published online June 5, 2017 [\[ARTICLE\]](#)
- [128 a b](#) Menter DG, Sabichi AL, Lippman SM. Selenium effects on prostate cell growth. *Cancer Epidemiol Biomarkers Prev*. (2000) 11: 1171-82 [\[PUBMED\]](#)
- [129](#)Hu H, Jiang C, Ip C, Rustum YM, Lu J. Methylseleninic acid potentiates apoptosis induced by chemotherapeutic drugs in androgen-independent prostate cancer cells. *Clinical Cancer Research* (2005). 11: 2379-2388. [\[PUBMED\]](#)
- [130](#)Rayman MP. Selenium in cancer prevention: a review of the evidence and mechanism of action. *Proc Nutr Soc*. (2005) 64(4): 527-42 [\[PUBMED\]](#)
- [131](#)Zhao H, Brooks JD. Selenomethionine induced transcriptional programs in human prostate cancer cells. *J Urol*. (2007) 177(2): 743-50 [\[PUBMED\]](#)

- [132](#)Whanger PD. Selenium and its relationship to cancer: an update dagger. *British Journal of Nutrition* (2004). 91: 11-28. [[PUBMED](#)]
- [133 a b](#) Duffield-Lillico AJ, Dalkin BL, Reid ME, et al. Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: an analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial. *BJU Int.* (2003) 91(7): 608-12. [[PUBMED](#)]
- [134](#)A.J. Duffield-Lillico, B.L. Dalkin, M.E. Reid, B.W. Turnbull, E.H. Slate and E.T. Jacobs et al. Selenium supplementation, baseline plasma selenium status and incidence of prostate cancer: an analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial. *British Journal of Urology International.* (2003) 91: 608. [[PUBMED](#)]
- [135](#)Clark LC, Dalkin B, Krongrad A et al. Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. *British Journal of Urology* 1998; 81: 730-734 [[PUBMED](#)]
- [136 a b](#) Micke O, Schomburg L, Buentzel J, Kisters K, Muecke R. Selenium in oncology: from chemistry to clinics. *Molecules.* 2009 Oct 12;14(10):3975-88. [[PUBMED](#)]
- [137](#)Zu K, Ip C. Synergy between selenium and vitamin E in apoptosis induction is associated with activation of distinctive initiator caspases in human prostate cancer cells. *Cancer Research.* (2003) 63(20): 6988-95 [[PUBMED](#)]
- [138](#)Sun Q, Dong M, Wang Z, Wang C, Sheng D, Li Z, Huang D, Yuan C. Selenium-enriched polysaccharides from *Pyracantha fortuneana* (Se-PFPs) inhibit the growth and invasive potential of ovarian cancer cells by stopping  $\beta$ -catenin signaling. *Oncotarget.* 2016 Apr 6. [[PUBMED](#)]
- [139](#)Tagaram HR, Desai D, Li G, Liu D, Rountree CB, Gowda K, Berg A, Amin S, Staveley-O'Carroll KF, Kimchi ET. A Selenium Containing Inhibitor for the Treatment of Hepatocellular Cancer. *Pharmaceuticals (Basel).* 2016 Mar 24;9(2). [[PUBMED](#)]
- [140](#)Pfister C, Dawczynski H, Schingale FJ. Sodium selenite and cancer related lymphedema: Biological and pharmacological effects. *J Trace Elem Med Biol.* 2016 Sep;37:111-6. [[PUBMED](#)]
- [141](#)Zeng H1, Wu M. The Inhibitory Efficacy of Methylseleninic Acid Against Colon Cancer Xenografts in C57BL/6 Mice. *J Trace Elem Med Biol.* 2016 Sep;37:111-6. [[PUBMED](#)]
- [142](#)Plant profile for Cannabis sativa from the USDA. Accessed 04-10-2013 <http://plants.usda.gov/java/profile?symbol=casa3>
- [143 a b](#) Adams IB, Martin BR. Cannabis: pharmacology and toxicology in animals and humans. *Addiction.* 1996 Nov;91(11):1585-614. [[PUBMED](#)]
- [144 a b](#) Sharma P, Murthy P, Bharath MM. Chemistry, metabolism, and toxicology of cannabis: clinical implications. *Iran J Psychiatry.* 2012 Fall;7(4):149-56. [[PUBMED](#)]
- [145](#)Resstel LB, Tavares RF, Lisboa SF, Joca SR, Corrêa FM, Guimarães FS. 5-HT1A receptors are involved in the cannabidiol-induced attenuation of behavioural and cardiovascular responses to acute restraint stress in rats. *Br J Pharmacol.* 2009 Jan;156(1):181-8. doi: 10.1111/j.1476-5381.2008.00046.x. [[PUBMED](#)]
- [146 a b](#) Alexander A, Smith PF, Rosengren RJ. Cannabinoids in the treatment of cancer. *Cancer Lett.* 2009 Nov 18;285(1):6-12. doi: 10.1016/j.canlet.2009.04.005. Epub 2009 May 12. [[PUBMED](#)]
- [147 a b c](#) Preet A, Qamri Z, Nasser MW, Prasad A, Shilo K, Zou X, Groopman JE, Ganju RK. Cannabinoid receptors, CB1 and CB2, as novel targets for inhibition of non-small cell lung cancer growth and metastasis. *Cancer Prev Res (Phila).* 2011 Jan;4(1):65-75. doi: 10.1158/1940-6207.CAPR-10-0181. Epub 2010 Nov 19. [[PUBMED](#)]
- [148 a b c](#) Qamri Z, Preet A, Nasser MW, Bass CE, Leone G, Barsky SH, Ganju RK. Synthetic cannabinoid receptor agonists inhibit tumor growth and metastasis of breast cancer. *Mol Cancer Ther.* 2009 Nov;8(11):3117-29. doi: 10.1158/1535-7163.MCT-09-0448. Epub 2009 Nov 3. [[PUBMED](#)]
- [149 a b c](#) McKallip RJ, Nagarkatti M, Nagarkatti PS. Delta-9-tetrahydrocannabinol enhances breast cancer growth and metastasis by suppression of the antitumor immune response. *J Immunol.* 2005 Mar 15;174(6):3281-9. [[PUBMED](#)]
- [150](#)De Petrocellis L, Ligresti A, Schiano Moriello A, Iappelli M, Verde R, Stott CG, Cristino L, Orlando P, Di Marzo V. Non-THC cannabinoids inhibit prostate carcinoma growth in vitro and in vivo: pro-apoptotic effects and underlying mechanisms. *Br J Pharmacol.* 2013 Jan;168(1):79-102. doi: 10.1111/j.1476-5381.2012.02027.x. [[PUBMED](#)]
- [151](#)Holler JM, Bosy TZ, Dunkley CS, Levine B, Past MR, Jacobs A. Delta9-tetrahydrocannabinol content of commercially available hemp products. *J Anal Toxicol.* 2008 Jul-Aug;32(6):428-32. [[PUBMED](#)]
- [152](#)Guzmán M, Duarte MJ, Blázquez C, Ravina J, Rosa MC, Galve-Roperh I, Sánchez C, Velasco G, González-Feria L. A pilot clinical study of Delta9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme. *Br J Cancer.* 2006 Jul 17;95(2):197-203. Epub 2006 Jun 27. [[PUBMED](#)]
- [153](#)GW Pharmaceuticals Ltd. A Study of Sativex® for Pain Relief in Patients With Advanced Malignancy. (SPRAY). www.clinicalTrials.gov. Identifier: NCT00530764. 2013. [<https://clinicaltrials.gov/ct2/show/results/NCT00530764?term=THC+cancer&rank=6&sect=Xfedcba987016#limit>]
- [154 a b](#) Hermanson DJ, Marnett LJ. Cannabinoids, endocannabinoids, and cancer. *Cancer Metastasis Rev.* 2011 Dec;30(3-4):599-612. doi: 10.1007/s10555-011-9318-8. [[PUBMED](#)]
- [155 a b](#) Bowles DW, O'Bryant CL, Camidge DR, Jimeno A. The intersection between cannabis and cancer in the United States. *Crit Rev Oncol Hematol.* 2012 Jul;83(1):1-10. Epub 2011 Oct 21. [[PUBMED](#)]
- [156](#)Salazar M, Lorente M, García-Taboada E, Hernández-Tiedra S, Davila D, Francis SE, Guzmán M, Kiss-Toth E, Velasco G. The pseudokinase tribbles homologue-3 plays a crucial role in cannabinoid anticancer action. *Biochim Biophys Acta.* 2013 Apr 5. pii: S1388-1981(13)00085-1 [Epub ahead of print] [[PUBMED](#)]
- [157](#)Todaro B. Cannabinoids in the treatment of chemotherapy-induced nausea and vomiting. *J Natl Compr Canc Netw.* 2012 Apr;10(4):487-92. [[PUBMED](#)]
- [158](#)Glare P, Miller J, Nikolova T, Tickoo R. Treating nausea and vomiting in palliative care: a review. *Clin Interv Aging.*

- 2011;6:243-59. Epub 2011 Sep 12. [PUBMED]
- [159](#)Carter GT, Flanagan AM, Earleywine M, Abrams DI, Aggarwal SK, Grinspoon L. Cannabis in palliative medicine: improving care and reducing opioid-related morbidity. *Am J Hosp Palliat Care*. 2011 Aug;28(5):297-303. Epub 2011 Mar 28.
  - [160](#)Scott KA, Dagleish AG, Liu WM. The combination of cannabidiol and 9-tetrahydrocannabinol enhances the anticancer effects of radiation in an orthotopic murine glioma model. *Mol Cancer Ther*. 2014 Dec;13(12):2955-67. [PUBMED]
  - [161](#)PDQ® Integrative, Alternative, and Complementary Therapies Editorial Board. PDQ Cannabis and Cannabinoids. Bethesda, MD: National Cancer Institute. Updated 05/27/2016. Available at: <http://www.cancer.gov/about-cancer/treatment/cam/hp/cannabis-pdq>. Accessed 06/20/2016. [<http://www.cancer.gov/about-cancer/treatment/cam/hp/cannabis-pdq>]
  - [162](#)Zick SM, Sen A, Feng Y, Green J, Olatunde S, Boon H. Trial of Essiac to ascertain its effect in women with breast cancer (TEA-BC). *J Altern Complement Med*. (2006) 10: 971-80 [PUBMED]
  - [163](#)Kulp KS, Montgomery JL, Nelson DO, Cutter B, Latham ER, Shattuck DL, Klotz DM, Bennett LM. Essiac and Flor-Essence herbal tonics stimulate the in vitro growth of human breast cancer cells. *Breast Cancer Res Treat*. (2006) 98(3): 249-59 [PUBMED]
  - [164 a b](#) Ottenweller J, Putt K, Blumenthal EJ, Dhawale S, Dhawale SW. Inhibition of prostate cancer-cell proliferation by Essiac. *J Altern Complement Med*. (2004) 10(4): 687-91. [PUBMED]
  - [165 a b](#) Tai J, Cheung S, Wong S, Lowe C. In vitro comparison of Essiac and Flor-Essence on human tumor cell lines. *Oncol Rep*. (2004) 11(2): 471-6 [PUBMED]
  - [166](#)Cassie RM. The Story of Essiac: Her Healing Journey. The Resperin Corporation, Waterloo, Ontario, Canada. Accessed 6/1/2010. [<http://www.resperin.ca/>]
  - [167 a b](#) Kulp KS, Montgomery JL, Nelson DO, Cutter B, Latham ER, Shattuck DL, Klotz DM, Bennett LM. Essiac and Flor-Essence herbal tonics stimulate the in vitro growth of human breast cancer cells. *Breast Cancer Res Treat*. (2006) 98(3): 249-59 [PUBMED]
  - [168](#)Leonard SS, Keil D, Mehlman T, Proper S, Shi X, Harris GK. Essiac tea: scavenging of reactive oxygen species and effects on DNA damage. *J Ethnopharmacol*. (2006) 103(2): 288-96. [PUBMED]
  - [169](#)Leonard SS, Keil D, Mehlman T, Proper S, Shi X, Harris GK. Essiac tea: scavenging of reactive oxygen species and effects on DNA damage. *J Ethnopharmacol*. (2006) 103(2): 288-96. [PUBMED]
  - [170](#)Zick SM, Sen A, Feng Y, Green J, Olatunde S, Boon H. Trial of Essiac to ascertain its effect in women with breast cancer (TEA-BC). *J Altern Complement Med*. (2006) 10: 971-80 [PUBMED]
  - [171](#)National Library of Medicine. 2016. ClinicalTrials.gov Retrieved 22 June 2016 from the National Institutes of Health Web Site: <http://www.clinicaltrials.gov/ct/search;jsessionid=77C2E74E90EC0B1C27B8F039E1FA6244?term=Essiac%2C+cancer&submit=Search>
  - [172](#)PDQ® Integrative, Alternative, and Complementary Therapies Editorial Board. PDQ Essiac/Flor Essence. Bethesda, MD: National Cancer Institute. Updated 20 Aug 2015. Available at: <http://www.cancer.gov/about-cancer/treatment/cam/hp/essiac-pdq>. Accessed 22 June 2016. [<http://www.cancer.gov/about-cancer/treatment/cam/hp/essiac-pdq>] [PUBMED]
  - [173](#)US Food and Drug Administration website. Accessed 6/20/2016. [<http://www.fda.gov/>]
  - [174](#)PDQ® Integrative, Alternative, and Complementary Therapies Editorial Board. PDQ Essiac/Flor Essence. Bethesda, MD: National Cancer Institute. Updated 20 Aug 2015. Available at: <http://www.cancer.gov/about-cancer/treatment/cam/hp/essiac-pdq>. Accessed 22 June 2016. [<http://www.cancer.gov/about-cancer/treatment/cam/hp/essiac-pdq>] [PUBMED]
  - [175](#)Gerson Institute website [<http://gerson.org/gerpress/about-us/>]
  - [176](#)PDQ® Integrative, Alternative, and Complementary Therapies Editorial Board. PDQ Gerson Therapy. Bethesda, MD: National Cancer Institute. Updated 04-11-2016. Accessed 06-08-2016. [<http://www.cancer.gov/about-cancer/treatment/cam/hp/gerson-pdq>] [PUBMED]
  - [177](#)Cassileth B. Complementary therapies, herbs, and other OTC agents. *Oncology (Williston Park)*. 2008 Sep;22(10):1202. [PUBMED]
  - [178 a b](#) L. Taylor. Technical Data Report for Graviola: Annona Muricata. Sage Press, Inc. Herbal Secrets of the Rainforest second ed., 2002. [<http://www.rain-tree.com/reports/graviola-techreport.pdf>]
  - [179](#)Le Ven J, Schmitz-Afonso I, Lewin G, Lapr  vote O, Brunelle A, Touboul D, Champy P. Comprehensive characterization of Annonaceous acetogenins within a complex extract by HPLC-ESI-LTQ-Orbitrap   using post-column lithium infusion. *J Mass Spectrom*. 2012 Nov;47(11):1500-9. [PUBMED]
  - [180](#)Liaw CC, Wu TY, Chang FR, Wu YC. Historic perspectives on Annonaceous acetogenins from the chemical bench to preclinical trials. *Planta Med*. 2010 Sep;76(13):1390-404. Epub 2010 Jun 24. [PUBMED]
  - [181](#)de Pedro N, Cautain B, Melguizo A, Vicente F, Genilloud O, Pel  jez F, Tormo JR. Mitochondrial complex I inhibitors, acetogenins, induce HepG2 cell death through the induction of the complete apoptotic mitochondrial pathway. *J Bioenerg Biomembr*. 2013 Feb;45(1-2):153-64. Epub 2012 Nov 21. [PUBMED]
  - [182 a b](#) Torres Rachingani S, Purohit V, Pandey P, Joshi S, Moore ED, Johansson SL, Singh PK, Ganti AK, Batra SK. Graviola: a novel promising natural-derived drug that inhibits tumorigenicity and metastasis of pancreatic cancer cells in vitro and in vivo through altering cell metabolism. *Cancer Lett*. 2012 Oct 1;323(1):29-40. [PUBMED]
  - [183](#)L  pez-L  jzaro M, Mart  n-Cordero C, Bermejo A, Cortes D, Ayuso MJ. Cytotoxic compounds from Annonaceus species as DNA topoisomerase I poisons. *Anticancer Res*. 2001 Sep-Oct;21(5):3493-7. [PUBMED]
  - [184](#)Calder  n-Monta  o JM, Burgos-Mor  n E, Orta ML, Pastor N, Austin CA, Mateos S, L  pez-L  jzaro M. Alpha, beta-

- unsaturated lactones 2-furanone and 2-pyrone induce cellular DNA damage, formation of topoisomerase I- and II-DNA complexes and cancer cell death. *Toxicol Lett.* 2013 Jul 15. pii: S0378-4274(13)01131-4. [Epub ahead of print] [\[PUBMED\]](#)
- [185](#)Deep G, Kumar R, Jain AK, Dhar D, Panigrahi GK, Hussain A, Agarwal C, El-Elimat T, Sica VP, Oberlies NH4, Agarwal R. Graviola inhibits hypoxia-induced NADPH oxidase activity in prostate cancer cells reducing their proliferation and clonogenicity. *Sci Rep.* 2016 Mar 16;6:23135. [\[PUBMED\]](#)
  - [186](#)Magadi VP, Ravi V, Arpitha A, Litha, Kumaraswamy K, Manjunath K. Evaluation of cytotoxicity of aqueous extract of Graviola leaves on squamous cell carcinoma cell-25 cell lines by 3-(4,5-dimethylthiazol-2-Yl) -2,5-diphenyltetrazolium bromide assay and determination of percentage of cell inhibition at G2M phase of cell cycle by flow cytometry: An in vitro study. *Contemp Clin Dent.* 2015 Oct-Dec;6(4):529-33. [\[PUBMED\]](#)
  - [187](#)Dai Y, Hogan S, Schmelz EM, Ju YH, Canning C, Zhou K. Selective growth inhibition of human breast cancer cells by graviola fruit extract in vitro and in vivo involving downregulation of EGFR expression. *Nutr Cancer.* 2011;63(5):795-801. Epub 2011 Jun 22. [\[PUBMED\]](#)
  - [188](#)Hamizah S, Roslida AH, Fezah O, Tan KL, Tor YS, Tan CI. Chemopreventive potential of *Annona muricata* L leaves on chemically-induced skin papillomagenesis in mice. *Asian Pac J Cancer Prev.* 2012;13(6):2533-9. [\[PUBMED\]](#)
  - [189](#)Effect of *Annona Muricata* Leaves on Colorectal Cancer Patients and Colorectal Cancer Cells. 2015. Indonesia University. [Clinicaltrials.gov\[NCT02439580\]](https://clinicaltrials.gov/ct2/show/NCT02439580). [\[https://clinicaltrials.gov/ct2/show/NCT02439580?term=graviola&rank=1\]](https://clinicaltrials.gov/ct2/show/NCT02439580?term=graviola&rank=1)
  - [190](#)Caparros-Lefebvre D, Elbaz A. Possible relation of atypical parkinsonism in the French West Indies with consumption of tropical plants: a case-control study. Caribbean Parkinsonism Study Group. *Lancet.* 1999 Jul 24;354(9175):281-6. [\[PUBMED\]](#)
  - [191](#)Champy P, Melot A, GuÃ©rineau Eng V, Gleye C, Fall D, HÃ¶glinger GU, Ruberg M, Lannuzel A, LaprÃ©vote O, Laurens A, Hocquemiller R. Quantification of acetogenins in *Annona muricata* linked to atypical parkinsonism in guadeloupe. *Mov Disord.* 2005 Dec;20(12):1629-33. [\[PUBMED\]](#)
  - [192](#)Lannuzel A, HÃ¶glinger GU, Verhaeghe S, Gire L, Belson S, Escobar-Khondiker M, Poullain P, Oertel WH, Hirsch EC, Dubois B, Ruberg M. Atypical parkinsonism in Guadeloupe: a common risk factor for two closely related phenotypes? *Brain.* 2007 Mar;130(Pt 3):816-27. Epub 2007 Feb 15. [\[PUBMED\]](#)
  - [193](#)Lannuzel A, Haglinger GU, Champy P, Michel PP, Hirsch EC, Ruberg M. Is atypical parkinsonism in the Caribbean caused by the consumption of Annonaceae? *J Neural Transm Suppl.* 2006;(70):153-7. [\[PUBMED\]](#)
  - [194](#)Schapira AH. Complex I: inhibitors, inhibition and neurodegeneration. *Exp Neurol.* 2010 Aug;224(2):331-5. Epub 2010 Apr 1. [\[PUBMED\]](#)
  - [195](#)Champy P, Haglinger GU, FÃ©ger J, Gleye C, Hocquemiller R, Laurens A, GuÃ©rineau V, LaprÃ©vote O, Medja F, LombÃ©s A, Michel PP, Lannuzel A, Hirsch EC, Ruberg M. Annonacin, a lipophilic inhibitor of mitochondrial complex I, induces nigral and striatal neurodegeneration in rats: possible relevance for atypical parkinsonism in Guadeloupe. *J Neurochem.* 2004 Jan;88(1):63-9. [\[PUBMED\]](#)