Important Botanicals for the Prevention and Co-Management of Cancer

Lise Alschuler, ND

plant intelligence®
PROFESSIONAL RESOURCES

Table of Contents

Introduction

In the United States, one out of every four people will die from cancer. One in every two men and one in every three women will be diagnosed with cancer in their lifetime. The rampant spread of this disease begs the question: how can cancer be treated or prevented? There are a number of effective botanicals that are used in the prevention of cancer and its recurrence. But what are the roles of these botanicals in managing the toxicities of conventional cancer therapies? What types of research supports these claims? How do these botanicals compare to more traditional medicinal practices?

This paper will examine these questions and many more, looking at three botanical agents including:

1. Green tea (*Camellia sinensis*)
2. Turmeric (*Curcuma longa*)
3. Milk thistle (*Silybum marianum*)

The toll of cancer

In the next 20 years, cancer diagnoses are expected to increase by 45%. In 2010, 1.6 million people were diagnosed with cancer. In 2030, this number is estimated to increase to 2.3 million. Cancer rates are increasing globally and people are being diagnosed at younger and younger ages. But many people who are diagnosed also survive the disease. More than 12 million people have survived cancer treatment and are in need of ways to prevent cancer recurrence. This is an area where botanical medicines can be particularly effective.

Cancer treatment

With conventional treatment options, the overall survival rate from a cancer diagnosis in the 1940s increased from 25% to its current rate of about 54%. This is an improvement, but there are still improvements needed. Arguably, there is an opportunity to enhance the efficacy of conventional cancer treatments and promote an integrative approach. About 30% of the general population takes some form of dietary supplement on a regular basis while more than 80% of people diagnosed with cancer take supplements regularly. These statistics indicate that people with cancer understand that integrative treatment options can be beneficial. But with

approximately 50% of cancer patients not informing their oncologist about the natural medicines they are taking, interactions and ineffective supplements can have potentially negative effects.

Tipping the odds

Figure 1 is a linear representation of the carcinogenic process. This model can be an effective way to understand the efficacy of botanical therapies.

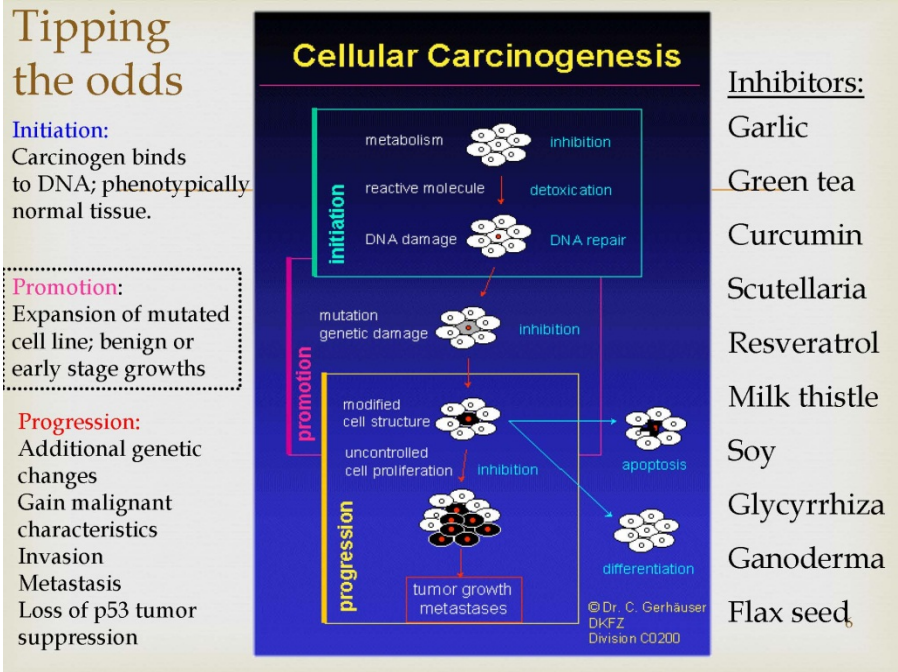


Figure 1

Carcinogenesis can be broken down into three stages:

1. Initiation
2. Promotion
3. Progression

In the initiation stage, preliminary damage to the DNA can occur. In addition to actual DNA mutations, this initiation stage can also consist of mutations in DNA expression, otherwise

known as epigenetic mutation. In general, this stage will result in some mutated expression from a DNA level of a population of cells.

As those cells begin to divide and replicate, they enter into the second stage: promotion. This is where the cells begin to expand and phenotypic changes occur. Some typical signs might be the presence of a lump or some other phenotypic change. As those cells continue to survive in a cluster, they gain additional aggressive characteristics and subsequently gain additional mutations, allowing them to survive and further facilitate their survival. Once the cells advance to the progression stage they begin to invade further into the tissue in which they are located and spread to other parts of the body. These events happen within a cell line and occur over a period of time. It is thought that this process occurs over several decades.

Chemoprevention: targets

Chemoprevention is a term that specifically refers to the use of natural substances to help prevent or delay the course of cancer, or the process of cancer causation. Carcinogens bind to proteins, DNA or RNA material in the cell, initiating the cell and causing the initial mutation. When this DNA is mutated, the mitochondria are mutated as well, creating the resulting initiated cell. This mitochondrial damage is an important part of the carcinogenic process.

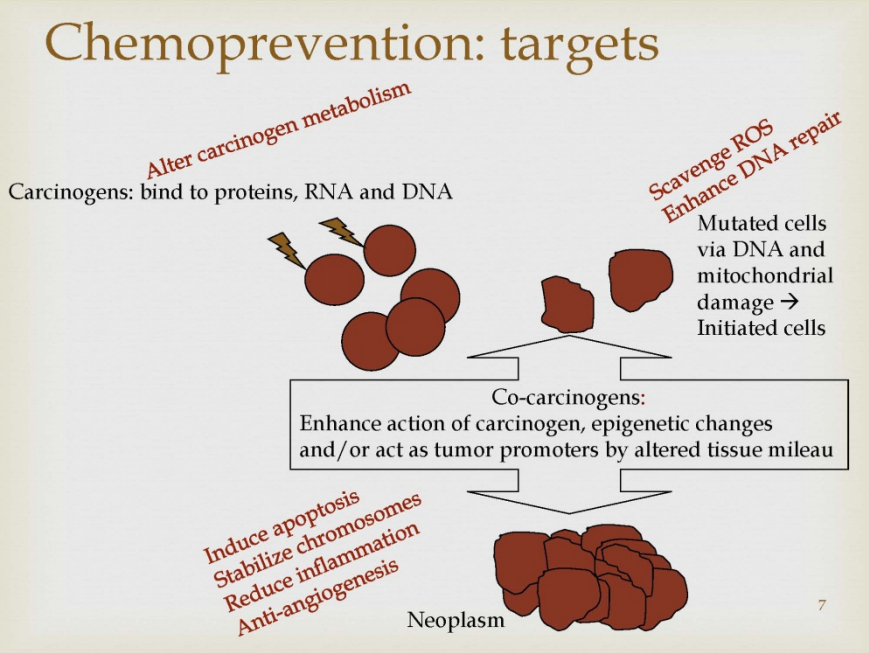


Figure 2

From here, co-carcinogens develop. These initiated cells do not typically survive and instead undergo apoptosis (a type of programmed cell suicide) unless some other co-carcinogenic process comes along and facilitates their survival. This is typically done by adding additional mutations that are compatible with increased aggressiveness, proliferation and angiogenesis. These co-carcinogens are usually environmental to the cell, and include carcinogenic environmental toxins. They can also include inflammatory cytokines and several other compounds that can facilitate this co-carcinogenic process. This environment typically leads to a neoplasm or cancer.

Therapeutic potential of botanicals in oncology

Cancer care can be thought of in three different areas:

1. Chemoprevention — often shortened to just prevention or risk reduction.
2. Co-management — the stage when people are actually receiving chemotherapy, radiation or other conventional treatment methods.
3. Antineoplastic — herbs with direct anti-cancer activities.

Botanicals are the most effective as preventive agents and work best in the co-management stage. Herbs are least effective as direct anti-cancer agents. Although there are cases in the literature of people who have undergone a so-called “spontaneous remission” or resolution of their cancer solely with the use of natural therapies, botanicals among them, this is rare.

Clinically relevant botanical agents in cancer care

The goal of botanical therapies and other integrative therapies are three-fold. First, the intent is to alter carcinogen metabolism. For example, can things that would otherwise damage DNA or the expression of DNA be prevented? Second, how can oxidative or damaging agents that have made their way into the cell be scavenged so they are not able to do damage in the cell? Are there ways to enhance the ability of DNA to repair itself from the damage it has sustained? Lastly, are there any ways to encourage these cells to go down the apoptotic pathway? Are there

ways to reduce their inflammation in order to reduce other co-carcinogenic influences or blood supply to the area?

Some of the most effective herbs that can help treat cancer include:

1. Green tea (*Camellia sinensis*)
2. Turmeric (*Curcuma longa)*
3. Milk thistle (*Silybum marianum*)
4. Ashwaghanda (*Withania somnifera*)
5. Magnolia (*Magnolia officinalis*)
6. Chinese skullcap (*Scutellaria baicalensis*)
7. Chamomile (*Matricaria recutita*)
8. Slippery elm (*Ulmus fulva*)
9. Ginseng (*Panax spp*.)
10. Andographis (*Andrographis paniculata*)
11. Ginkgo (*Ginkgo biloba*)

Though each of these herbs has a specific benefit, the top three most effective herbs in the area of cancer are green tea, turmeric and milk thistle.

Green tea (*Camellia sinensis*)

Green tea is most widely known for its high number of polyphenols, the most noted of which is epigallocatechin gallate (EGCG). Most of the research on green tea in the context of cancer care is done on an EGCG extract.

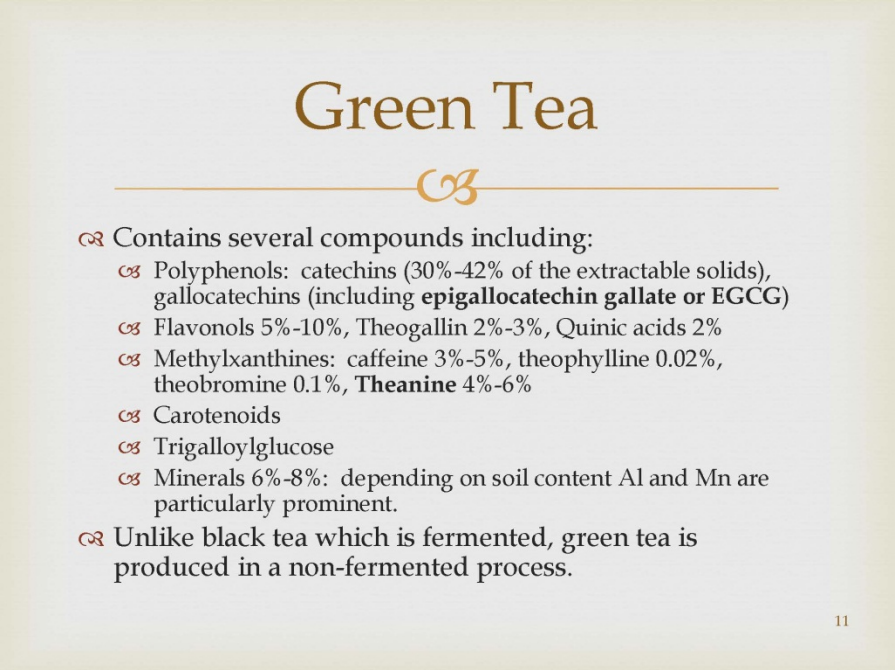


Figure 3

Green tea polyphenols have been shown to inhibit every step of carcinogenesis. Green tea supports the induction of the phase II enzymes that stimulate detoxification. It helps to reduce or modify carcinogens so they become less carcinogenic. It also stimulates DNA repair, reducing the amount of DNA damage. If cell damage has taken place, green tea induces apoptosis of those damaged cells. If a tumor is already growing, green tea inhibits growth signals, making it harder for the tumor to spread through the tissue. Finally, green tea reduces angiogenesis or increased blood flow to the tumor.

Detoxification

EGCG is known to inhibit the cytochrome P450 enzyme activation of procarcinogens. Many carcinogens are actually not carcinogenic until they undergo phase I detoxification, when they then become carcinogens. Green tea inhibits the enzymes that push these carcinogens into their more dangerous state. It also enhances phase II enzymes that help to conjugate those carcinogenic products from phase I.

Green tea has been shown to inhibit cytochrome p450-dependent metabolic activation of promutagens. It also helps with the detoxification of mutagens via induction of glutathione and other phase II enzymes.[1, 2, 3]

Green tea polyphenols capture and detoxify radicals of various promoters of carcinogenesis and radicals produced from exposure to radiation and light. This antioxidant effect has also been demonstrated in humans. A study evaluated urinary and WBC markers of oxidative stress in smokers and non-smokers, comparing them to a control group.[4] The subjects of the trial consumed three grams of green tea three times a day for a week. The green tea group was found to have significantly less oxidative DNA damage as noted by urinary markers than did non-tea drinkers. This was evident in both smokers and non-smokers, but clearly most evident in smokers because of their regular, increased consumption of carcinogens.[5]

DNA repair

Green tea repairs DNA. When carcinogens cause damage, EGCG has been shown to upregulate the production of cell repair proteins. Green tea does this by stimulating the genes that produce those proteins.[6] Green tea encourages apoptosis of damaged cells. It also boosts the production or activity of genes that pause cells. When these cells are not dividing as quickly, they pause and allow pro-apoptotic pathways to kick in.

Green tea activates capsase proteases. These enzymes form a cascade that ultimately causes the demise of the cell. Thus, green tea is an important protectant of the apoptotic pathway in cells. This has been demonstrated in normal cells as well as in malignant cells. A study showed that rats exposed to heterocyclic amines demonstrated significantly reduced mutagenicity and increased DNA repair in hepatocytes when fed green tea extract.[7]

Epigenetics

Cancer cells have altered patterns of gene expression. Cell-repair genes are critical in the protection against cancer development. Tumors that have been removed from people with cancer will show silenced cell repair genes. These genes are silenced by hypermethylation. There are numerous methyl groups that are stuck on those cell repair genes, particularly in CpG islands.

---

[1] Kuroda and Hara, Mutation Res 436:69, 1999
[2] Lin, et al, Biochem Pharmacol,1999.
[3] Fujiki, et al, Cancer Detect Preven, 2000.
[4] Ebata et al, Mutagen Res, 20:45, 1998.
[5] Klaunig et al, P.S.E.B.M., 220:249, 1999.
[6] Kuroda and Hara, Mutation Res 436:69, 1999.
[7] Weisburger et al, Princess Takamatsu Symp, 23:240, 1995.

CpG islands are regions right before the cell repair genes that have to be unsilenced in order for the cell repair gene to be read.

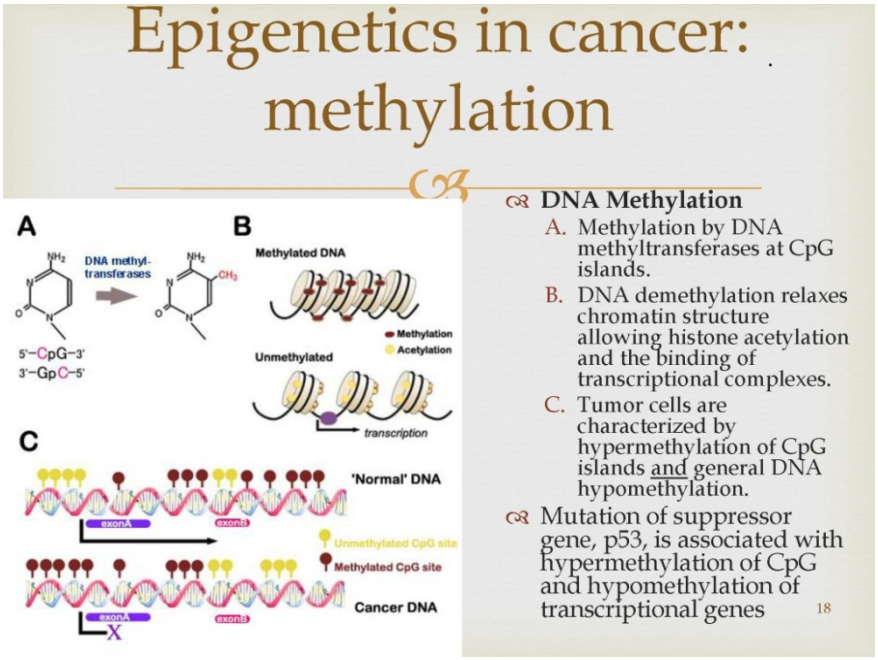


Figure 4

In cancer, cell repair genes are silenced because they are over methylated. The EGCG in green tea has been shown to inhibit DNA methyltransferase enzymes that add methyl groups to CpG islands. By inhibiting this enzyme, EGCG unmethylates cell repair genes. This is thought to be one of the ways in which regular consumption of green tea promotes cell repair activity since it gives the body a chance to activate genes involved in cell repair.[8]

Anti-proliferation

Green tea is also known as an anti-proliferant. It has been shown to inhibit topoisomerase, an enzyme that uncoils the DNA helix, allowing the DNA to be replicated in the course of cell division. Inhibiting this enzyme disallows cell replication and cell proliferation. EGCG is also known to silence many genes that are directly involved in transcription or cell proliferation.[9, 10]

---

[8] Manoharan N, et al. Int. braz j urol. [online]. 2007;33(1):11-18.
[9] Berger, et al, Biochem Biophys Res Commun, 2001
[10] Adhami, et al, J. Nutr, 2003

Green tea hinders metastasis by inhibiting the expression of genes involved in increased invasiveness of cancerous cells. This has been demonstrated in a variety of cell types, including stem cells that tend to have these genes over activated. In short, green tea interferes with every step of the carcinogenic pathway.

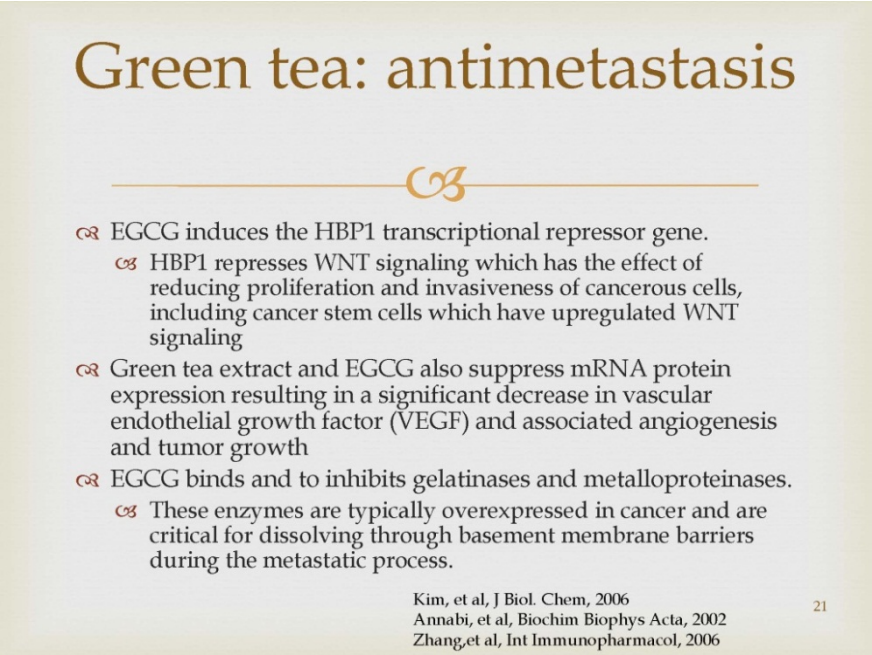


Figure 5

Pharmacokinetics

The bioavailability of orally consumed green tea polyphenols is low due to first pass, wide tissue distribution and incomplete absorption. Typically, significant cancer prevention effects are shown when people consume about ten four-ounce cups of green tea per day.

A phase I/II study of human volunteers demonstrated that a single dose of 1.2g of standardized green tea powder, equivalent to two to three cups of brewed tea (depending upon the strength of the tea) resulted in significant levels of tea polyphenols in plasma, urine and rectal biopsy samples. The half-life for green tea flavonoids is about four hours, which means that it would be necessary to get this dose at least three times a day to see any effects.[11, 12]

[11] Zhu, et al, Planta Med, 2000
[12] August, et al, Cancer Epidemiol Biomarkers Prev,1999

Bioavailability of green tea polyphenols in prostatectomy tissue

In a recent study, 17 individuals were randomized, consuming either green tea or water for a month. Researchers looked for green tea polyphenols in the blood during the intervention by taking prostate tissue samples. Green tea polyphenols were found in the prostatic tissue, with the majority (40-50%) found in the free form and 40-60% found as methylated EGCG.[13] These groups showed no elevation of liver function tests. Green tea may cause elevation of liver enzymes; however, this has been primarily documented in individuals taking high doses of green tea away from food. As a caution, when prescribing green tea it is best for it to be consumed with meals.

Dose escalation trial: polyphenon E and HR–breast cancer

A dose-escalation study looked at Polyphenon E (green tea extract) in hormone receptor-negative breast cancer. Women were given three different doses of the Polyphenon E daily for six months and had their breast tissue density assessed by a mammogram and core biopsy. All doses were well tolerated, and all doses produced pharmacological tissue levels of tea as measured in the urine. The results of this study indicate that the body does absorb and distribute some of the polyphenols in green tea.[14]

Epidemiological data

The epidemiological effects of green tea have been well documented. In 1988, a review concluded that green tea consumption was inversely correlated with pancreatic, colorectal, gastric and urinary bladder cancers. Additional studies have indicated that green tea is also preventative against prostate cancer. In all of these studies, at least five cups of green tea per day was needed in order to begin to see this preventive effect. Ten cups of green tea were associated with the strongest preventive effect in humans.[15, 16]

Meta-analysis

A 2008 meta-analysis of green tea evaluated 43 epidemiological studies, 4 randomized trials and 1 meta-analysis. More than half of the studies suggested that long-term consumption of green tea reduced the risk of many cancers, particularly gastrointestinal cancers. For unknown reasons, in these studies, women were found to receive slightly more benefit than men. The beneficial

---

[13] Wang P. et al. Cancer Prev Res (Phila) 2010;3(8):985.
[14] Crew KD, et al. Cancer Prev Res (Phila). 2012 5(9):1144.
[15] Bushman, Nutr Cancer,1998
[16] Jain et al, Int J Cancer,1998

effects, however, are not consistent across all studies. Thus, the interpretation of these findings is a challenge due to the significantly heterogeneous study designs, settings, populations, exposures, comparisons, outcome measures and potential publication biases.[17]

Clinical data

When looking at individual cancer cases, some interesting data can be found. One trial looked at premenopausal Japanese women who had been treated for breast cancer. They were followed for seven years after breast cancer surgery. Subjects were spread throughout stages I, II and III and divided up into two groups. The first group consumed less than four cups of green tea per day while the second consumed greater than five cups of green tea per day. In stages I and II, the recurrence rate in the first group was 24%. In the second group, the recurrence rate dropped to 16.7%, demonstrating a significantly reduced recurrence risk from higher green tea consumption. The disease-free survival in the first group was 2.8 years. For those who drank an average of seven cups of green tea a day, disease-free survival increased to 3.6 years. It is important to note that no statistical difference was noted in stage III cancer group, suggesting that green tea has recurrence prevention effects, but only in early stage cancers.

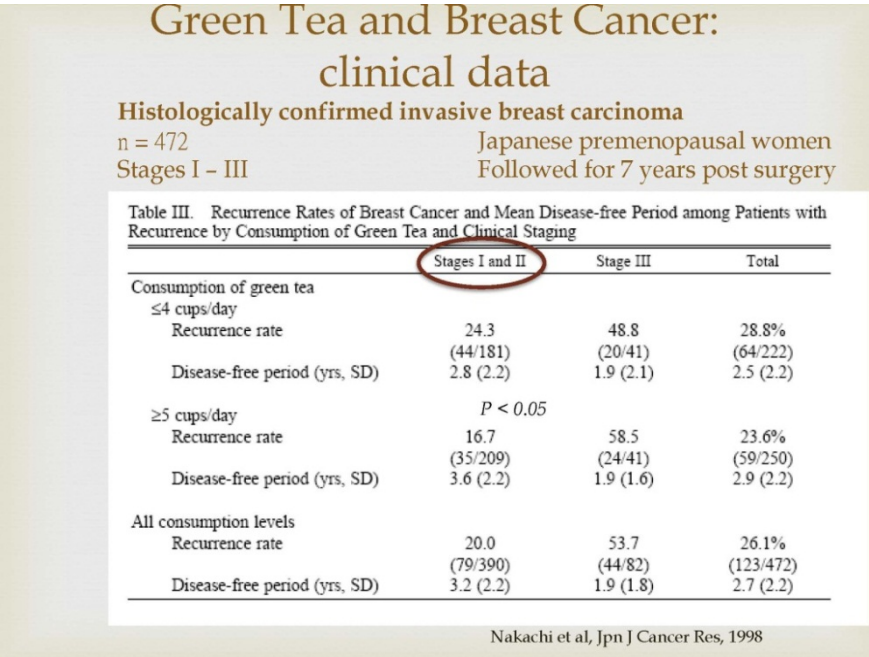


Figure 6

[17] Liu J, et al. Chinese Medicine. 2008;3:12

This was further documented in another prospective cohort trial. This nine-year trial looked at women who had invasive breast cancer that was definitively treated. These women consumed an average of five cups of green tea per day. In all stages, the hazard ratio was 0.69. In stage I, the reduction in risk was significant. In stage III and IV, there were no changes, suggesting that the effects of green tea are most likely limited to early stage breast cancers.

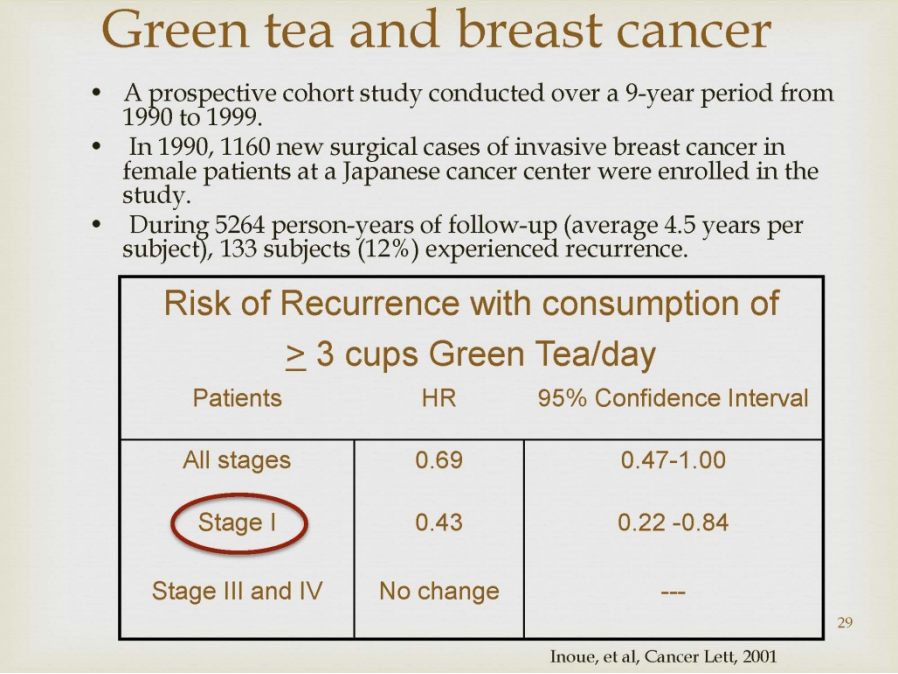


Figure 4

Prostate cancer

In prostate cancer, the effectiveness of green tea is more mixed. A double-blind, placebo-controlled, randomized trial of 60 men with high-grade prostate intraepithelial neoplasia (PIN) was recently conducted. Within the course of a year, typically 30% of these PINs will develop into prostate cancer. In this study, men with PIN were given 600mg of green tea catechins or a placebo. Researchers found that in the green tea group, only 3% converted into prostate cancer in a year versus the typical 30% in the placebo group, demonstrating the preventive effects of green tea in prostate cancer. Additionally, the International Prostate Symptom Score and quality of life

scores of the green tea treated men were significantly higher than in the placebo group. No adverse events were reported.[18]

Short term GTEx and prostate CA biomarkers

In another study, 26 men with positive prostate biopsies who were scheduled for prostatectomy were put on Polyphenon E with EGCG until the time of surgery. During the surgery, various factors in the tissue were examined. Hepatocyte Growth Factor, VEGF, PSA, IGF-1, IGFBP-3 and IGF/IGFBP-3 ratio all decreased significantly in the green tea consumers. Interestingly, liver function tests decreased as well.[19]

RDBPCT GTEx and prostate cancer

In a randomized, double-blind, placebo-controlled trial, men with prostate cancer were given Polyphenon E or placebo for three to six weeks prior to surgery. When the prostates were removed in these men, no polyphenols were present in the prostate tissue, but PSAs decreased. The Gleason scores were better, and they had less oxidative damage in their white blood cells. These findings clearly indicate that there is an effect on the overall behavior of prostate cancer.[20]

Colon cancer

Studies of green tea and colon cancer advocate the role of green tea as a preventive therapy. One study contained patients with a family history of colon cancer who were therefore at higher risk. Each patient in the study had part of the colon resected for polyps. In the portion of the colon retained, patients were given 5-fluorouracil suppositories. They were also given green tea extract orally. Slight regressions were found in the remaining polyps in the rectal segments still in the individual. In addition, none of the patients in the study developed rectal cancer. This is not an expected result, thus indicating a type of synergy between the 5-fluorouracil and the green tea extract. There was also less toxicity noted from using the 5-fluorouracil suppositories.[21, 22]

---

[18] Bettuzzi, et al, Cancer Res, 2006
[19] McLarty J. et al. Cancer Prev Res (Phila). 2009; 2(7):673.
[20] Nguyen NM, et al. Cancer Prev Res (Phila). 2012; 5(2):290-8.
[21] Clin Cancer Res. 2001 Dec;7(12):4220-9.
[22] Nippon Geka Gakkai Zasshi. 1998 Jun;99(6):391-5.

CLL

Phase I Trial

In a phase I trial, patients with previously treated chronic lymphocytic leukemia were given Polyphenon E in doses ranging from 400 to 2,000mg twice per day. One patient in this phase I trial experienced partial remission and 33% saw sustained reduction in lymphocyte count, one of the main markers of progression. Decreased lymph node size was shown in 92% of patients in this study.[23]

Phase II trial

The results of this study prompted a phase II trial. In the phase II trial, 42 patients who were previously untreated with an absolute lymphocyte count of greater than ten were given Polyphenon E at 2,000mg twice a day for up to six months. One third saw sustained reduction of over 20% in the absolute lymphocyte count. Around 69% who had palpable lymph nodes had at least a 50% reduction in the sum of all involved nodes. Overall, 70% of people had some form of biological response, a significant result. This result is particularly relevant because chronic lymphocytic leukemia is managed as a chronic disease, thus green tea has a potentially important role to play.[24]

Green tea and other cancers

Other studies have correlated green tea consumption with cancer incidence. For example, green tea consumption is inversely correlated with ovarian cancer incidence, with each cup of tea associated with an 18% lower risk of ovarian cancer.

---

[23] Shanafelt T, et al. J Clinical Oncology, 2009; 27(23):3808.

[24] Shanafelt, TD, et al. Cancer. 2012; Jul 3. Epub ahead of print

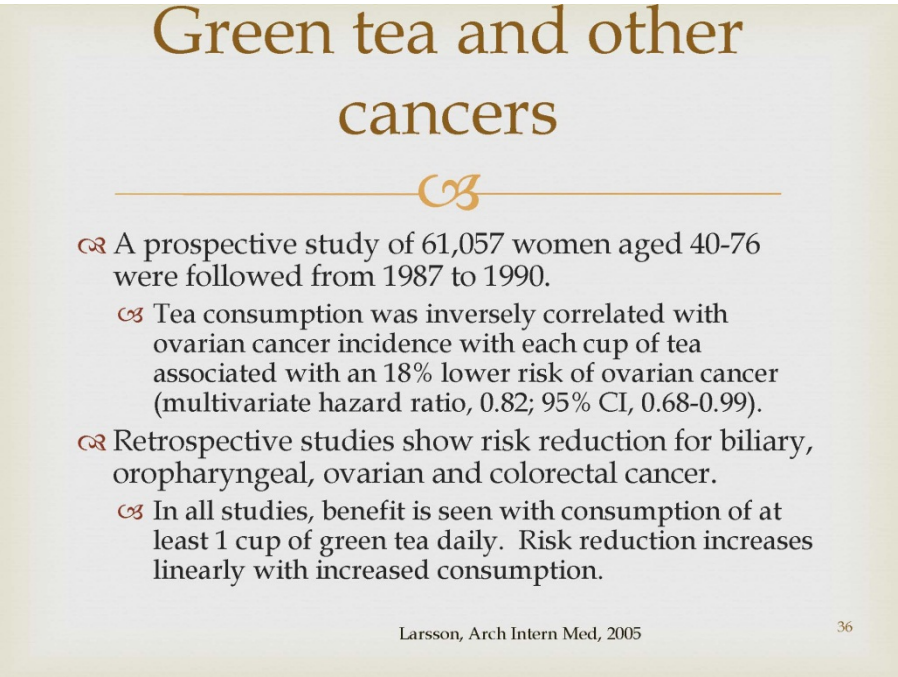


Figure 5

Green tea and chemotherapy

When it comes to co-management, green tea is very synergistic with a number of chemotherapeutics, notably Doxil or Adriamycin. Doxorubicin is a frequently used chemotherapy agent that is utilized in numerous cancers, including breast cancer. Green tea actually inhibits the ability of tumors to eject the Doxil, so it maintains sensitivity in the tumors to the chemotherapeutic effects. At the same time, it reduces the concentration of chemotherapy in organs, particularly the heart and the liver, the two organs that are most prone to Doxil or Adriamycin-induced toxicity.[25, 26, 27]

Green tea and Tamoxifen

Co-treatment with Tamoxifen and EGCG on human PC-9 lung cancer cells were shown to induce apoptosis more strongly than Tamoxifen or EGCG alone. In fact, Tamoxifen on its own

[25] Sadzuka, et al, Clin Cancer Res, 1998
[26] Sadzuka, et al, Toxicol Lett, 2000
[27] Luo T et al. Breast Cancer Res. 2010; 12(1):R8

was not effective at suppressing ER-negative tumor growth, whereas EGCG had a modest effect on tumor growth. A combination of the two drugs showed marked tumor suppression.[28, 29]

Turmeric (*Curcuma longa*)

Curcuma longa, or turmeric, is an important herb in the world of oncology. Preclinical data about turmeric is expansive. When discussing turmeric in the context of oncology, curcumin, one of the curcuminoids in turmeric root, dominates the area of clinical research. Evidence also suggests that whole turmeric root provides benefits as well, though it is less studied.

Curcumin from turmeric is one of the most biologically active and studied constituents in the world of botanicals. Curcumin affects almost every known target or molecule involved in carcinogenesis. It is highly biologically active on a molecular level, explaining its utility in a variety of cancers and as a general cancer preventative.

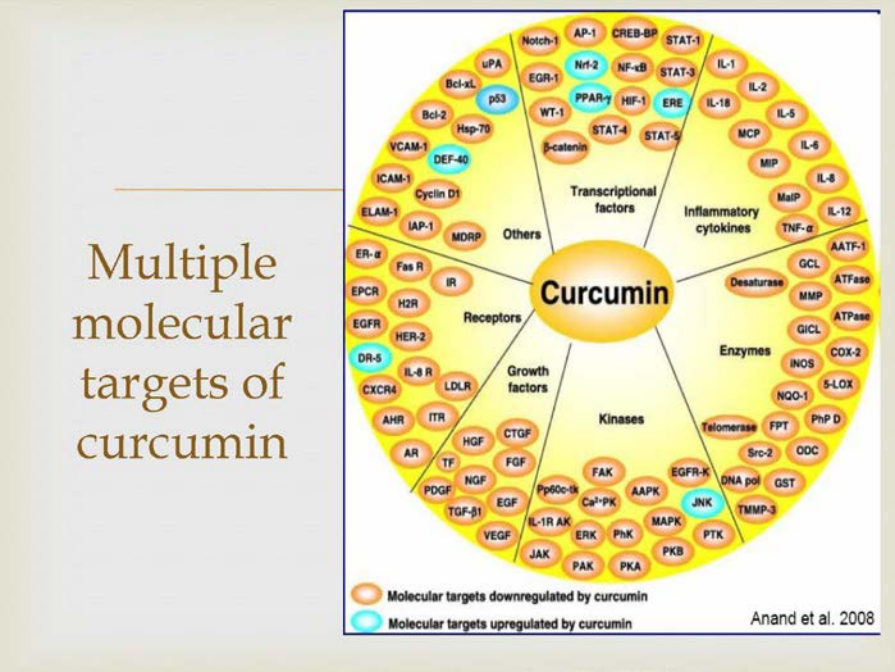


Figure 6

[28] Suganuma, et al, Cancer Res, 1999

[29] Scandlyn MJ et al. Briish J Cancer, 2008, 99:1056.

Anti-inflammation

Curcumin from turmeric is an extremely effective anti-inflammatory. It is a strong inhibitor of NF-kB, the master switch of inflammation. When NF-kB is released and activated, it upregulates almost all other inflammatory genes in the cell; therefore, inhibiting NF-kB is a highly effective means to reduce the inflammatory process.

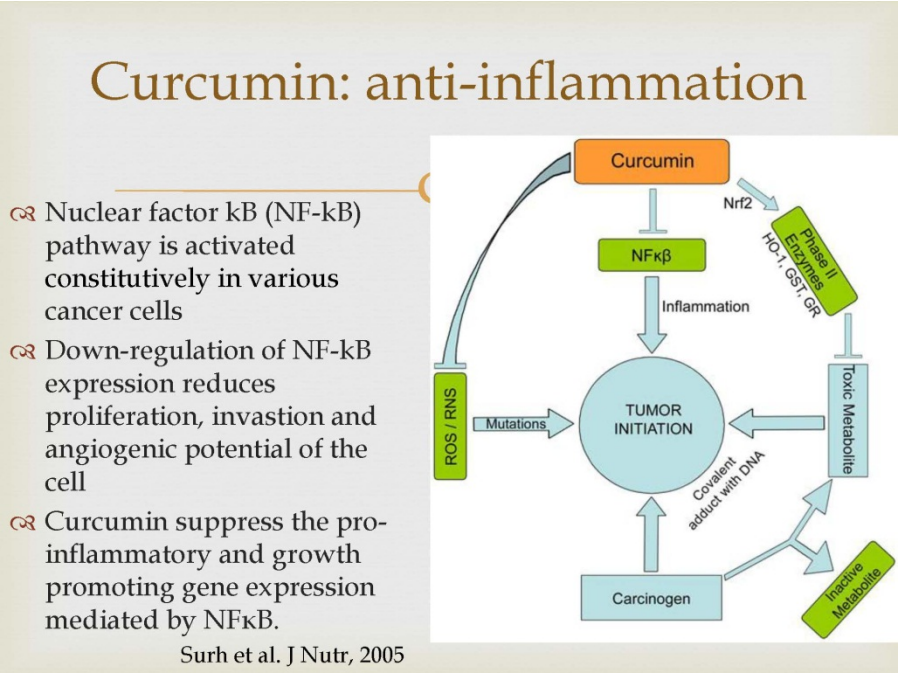


Figure 7

At the same time, curcumin also enhances Nrf2, a gene that upregulates phase II detoxification enzymes. Curcumin inhibits the inflammatory reaction, reducing the formation of toxic metabolites that would otherwise activate the inflammatory process. Curcumin itself acts as an antioxidant and quenches free radicals.

Detoxification

Curcumin can play an important role in detoxification through Nrf2 activation. It specifically upregulates glutathione transferases and other enzymes involved in phase II detoxification, making it a very effective detoxification agent.[30, 31]

Apoptosis

Curcumin plays an important role in the process of apoptosis by downregulating Bcl-2 and upregulating Bax through JNK pathway activation. When Bax is stimulated, anti-apoptosis is reduced, which allows the cell to undergo apoptosis. In other words, curcumin helps damaged cells kill themselves.[32]

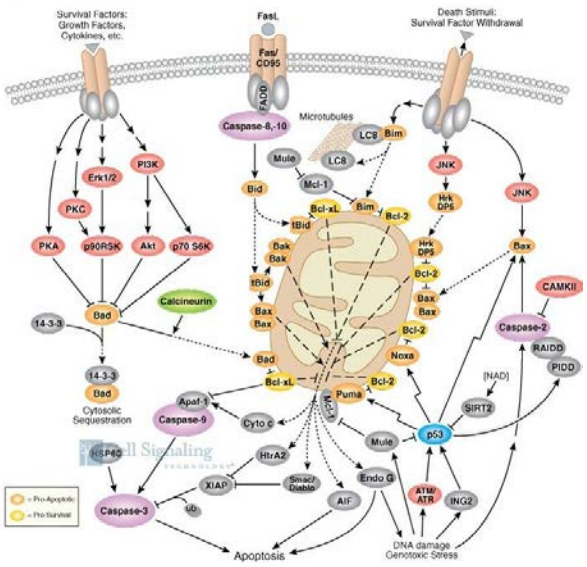


Figure 8

Cancerous cells tend to have upregulated pro-apoptotic gene patterns and, therefore, do not undergo apoptosis when they should. A number of clinical trials have demonstrated that curcumin can help bring balance back to the cell. In general, the higher the dose of curcumin, the more inhibition of cells, or the more apoptosis that occurs in these cancerous cell lines.

---

[30] Dinkova-Kostova and Talalay, Carcinogenesis 20(5):911:1999

[31] Somasundaram et al, Cancer Res, 62(13):3868, 2002.

[32] Iwashita, et al. Biosci Biotechnol Biochem, 2000

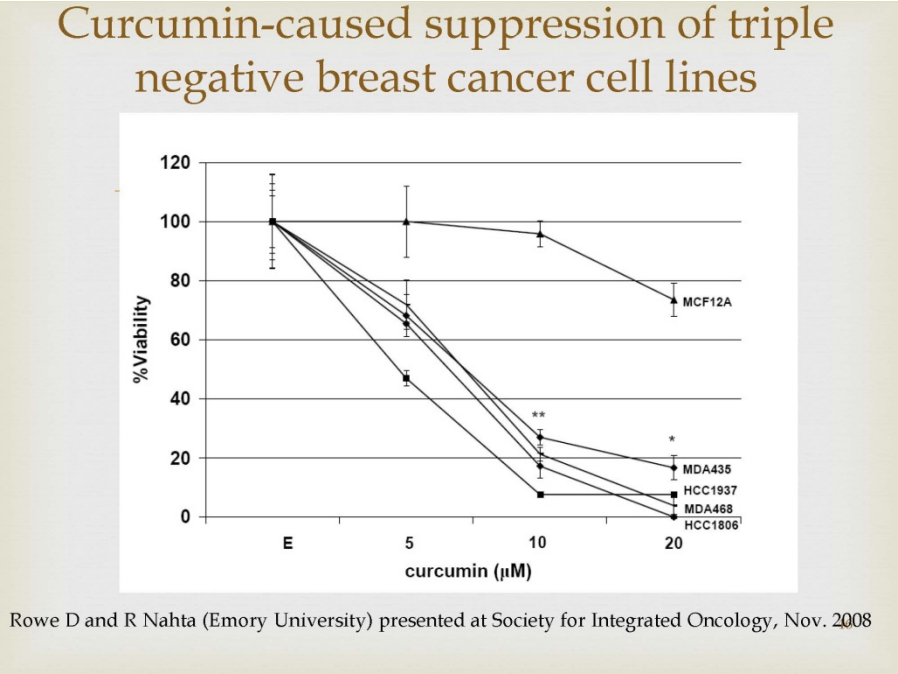


Figure 9

In addition to breast cancer, similar results have been shown in prostate cancer cells. Studies have shown that curcumin significantly inhibits prostate cancer growth and upregulates apoptosis in both androgen-dependent and androgen-independent cells.[33,34]

Anti-angiogenesis

Curcumin has strong anti-angiogenesis actions and inhibits VEGF by inhibiting the receptors that VEGF binds to. VEGF is secreted by both tumor cells as well as the tissue around tumor cells. Tumor cells co-opt the body, using the tissue to facilitate its own survival. Tumor cells send signals out to the tissue stroma to secrete more VEGF. VEGF then binds to receptors on blood vessels, causing those blood vessels to grow sprouts, essentially feeding the tumor. Thus, blocking those receptors is an important step in reducing blood supply to tumors because it chokes off any nutrition to the tumor, causing it to die.

[33] Prostate 2001;47:293-303
[34] Mol Urol 2000;4:1-6

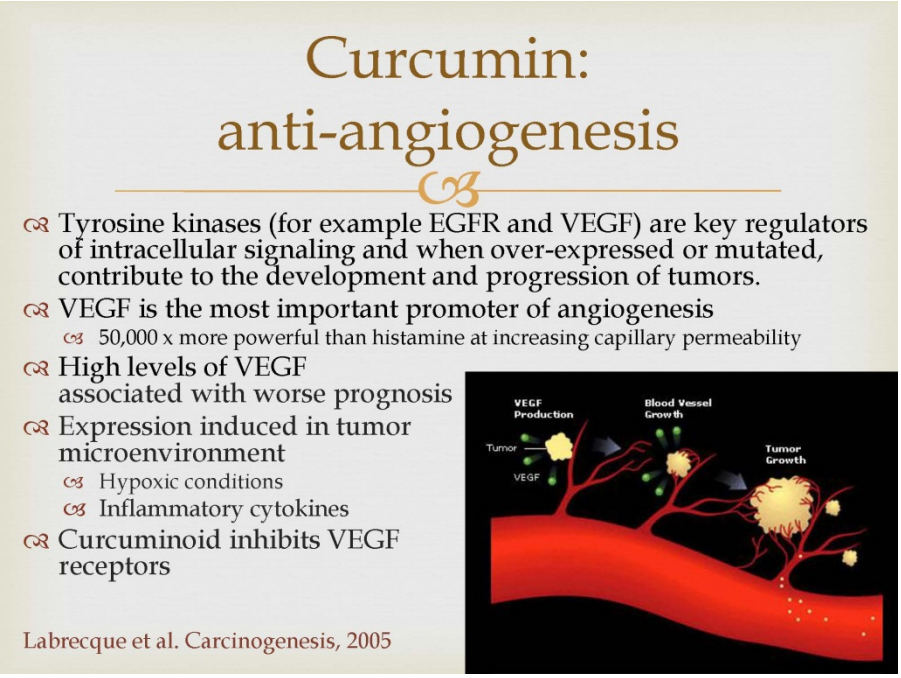


Figure 13

PPAR-γ

PPAR is an anti-inflammatory molecule in the cell. It is also an anti-angiogenic molecule. Curcumin is a PPAR agonist, meaning it upregulates PPAR by adding more anti-inflammation and anti-angiogenesis. This has been demonstrated in a clinical trial in humans with inflammatory, recurrent anterior uveitis. In this study, curcumin not only reduced the symptoms of the uveitis but specifically upregulated PPAR.[35]

Vitamin D receptor ligand

Curcumin acts as a vitamin D analogue, meaning when vitamin D binds to the vitamin D receptor on the surface of a cell, curcumin can take its place. This means, when someone is vitamin D deficient but takes curcumin, the curcumin will bind to the vitamin D and retinoid acid X receptors. Vitamin A and D are synergistic and translocate into the cytoplasm as a liganded vitamin D retinoic acid receptor. They release vitamin D, or in this case the curcumin, which binds to the receptor on the nuclear membrane. That causes the same translocation of the vitamin D (curcumin) to the nucleus, where it binds to the DNA and specifically vitamin D response

[35] P. Allegri, et al. Clinical Ophthalmology. 2010;4:1-6

elements. These then trigger the upregulation of certain genes which ultimately transcribe tumor suppressor activity, anti-inflammatory activity and also help regulate calcium levels.

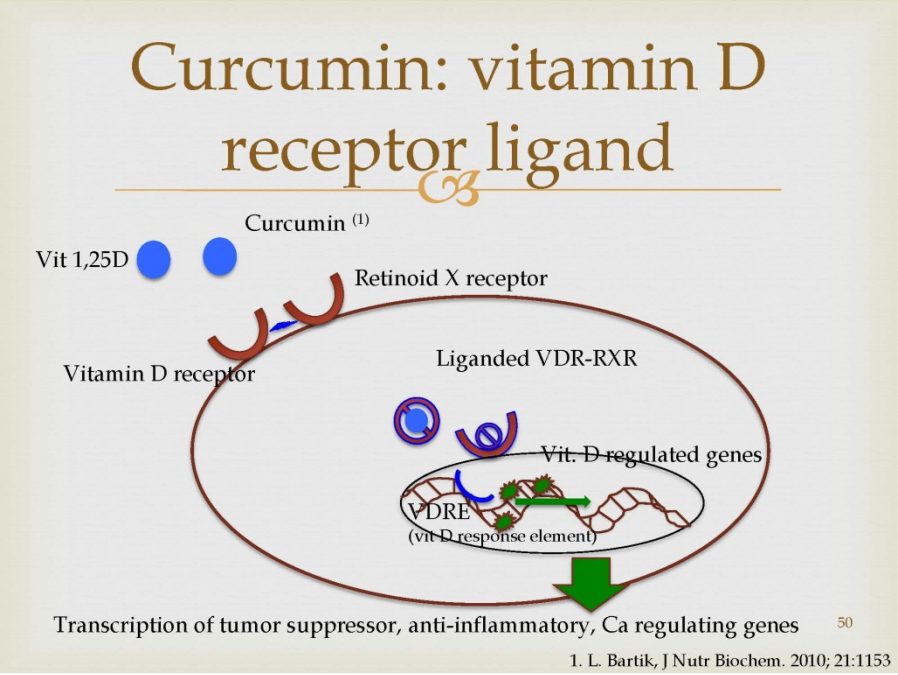


Figure 10

Pharmacology

From a pharmacological perspective, very little ingested curcumin is found in plasma. Ingesting 8 grams of pure curcumin, for example, will only yield 1-µg/mL of curcumin in the plasma. Several trials at MD Anderson suggest that the body may need as much as 500ng/mL in the blood for clinical antineoplastic effects to occur. So is it possible to get enough curcumin to actually induce all of the benefits possible?

A clinical trial included 12 healthy subjects who ate a high-fat breakfast followed by 10 or 12g of encapsulated curcuma powder (75% curcumin). No adverse effects were shown and no free curcumin was detected in the plasma; however, curucmin conjugates (curcumin glucuronide and curumin sulfate) were detected. These findings suggest that conjugates can become de-conjugated intracellularly.[36]

[36] Vareed S, et al. Cancer Epidemiol Biomarkers Prev 2008;17(6):1411.

Mode of administration

The forms and absorption rates of curcumin vary. For example, curcumin powder on its own is relatively unabsorbed but when it binds to black pepper extract, increased absorption occurs. This combination can be effective in terms of increasing curcumin absorption rate, but black pepper extract irritates the gastric mucosa. This allows for the absorption of more curcumin, but it can also cause absorption of other things in the gut, including potential toxins that might otherwise not gain entry. For this reason, long-term use of black pepper extract is not advised.

Curcumin and gemcitabine in pancreatic cancer

Several clinical studies have reviewed the effects of curcumin on pancreatic cancer. Two studies published in 2010 delivered different results. The first included 21 patients with advanced pancreatic cancer who were resistant to Gemzar. Subjects were given 8 grams of curcumin daily in combination with Gemzar. Researchers found there was an increased median survival. Expected median survival in this group was 70 days. Median survival in this group increased to 161 days.[37]

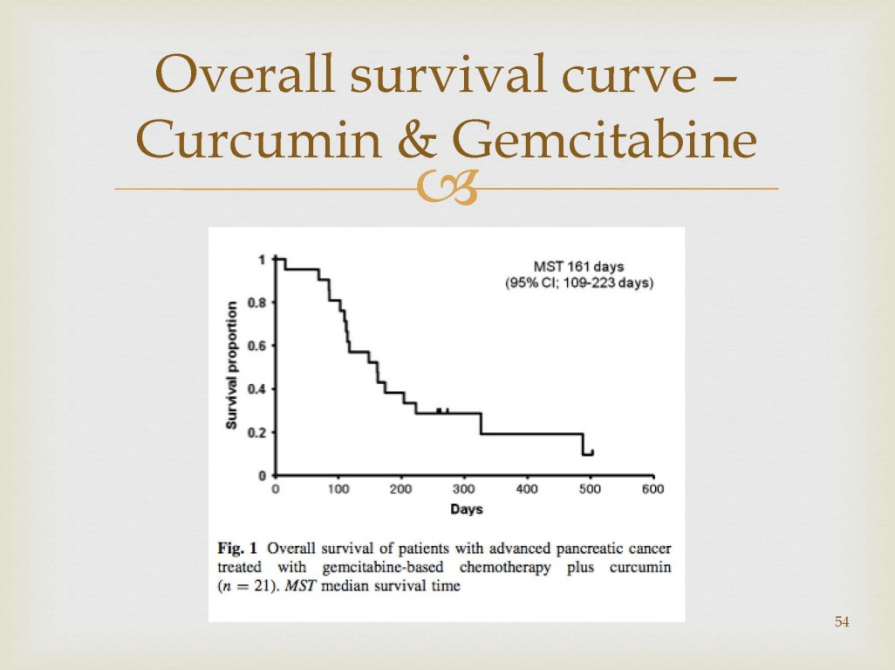


Figure 11

[37] Kanai M, et al. Cancer Chemother Pharmacol. 2010; Sept.

The second study evaluated the effects of curcumin in 17 patients with advanced pancreatic cancer. Results of the study showed that curcumin was not well tolerated by this group of people, nor was it clinically effective.[38] The mixed results from these two studies might suggest that the form used, dosage or the stage of cancer in which curcumin is administrated can have some effects on the efficacy of the herb.

Curcumin and colorectal cancer

In another study, 126 patients with colorectal cancer were randomized to participate. They received surgery, had radiotherapy, chemotherapy, chemoradiation therapy or no additional therapy. They were then further randomized to curcumin in addition to whatever therapy they received conventionally, or a placebo. Blood and tissue samples were analyzed pre and post. In the end, the body weight of those who received curcumin was found to be better than those in the placebo group. This is a significant finding since people with colorectal cancer who lose weight generally have worsening prognoses. The result was believed to be due to the fact that there was a 60% reduction in tumor necrosis factor alpha, one of the inflammatory genes controlled by NF-kB. Subjects showed reduced TNF-alpha production and therefore less cachexia. Furthermore, increased markers of apoptosis in the colon cancer cells were shown in patients receiving the curcumin.[39]

Curcumin and smoldering multiple myeloma

Multiple myeloma is a neoplastic disease of the plasma cells. There are two types of pre-multiple myeloma conditions: the first is monoclonal gammopathy of undetermined significance (MGUS) and the second is smoldering multiple myeloma. Both types are asymptomatic and over a period of up to 20 years can progress to multiple myeloma, a very serious, highly symptomatic and difficult to treat malignancy.

There are various ways this condition is analyzed, by looking at various markers. Curcumin inhibits the proliferation of multiple myeloma cells by down regulating various inflammatory genes. In a randomized, double-blind, placebo-controlled, crossover trial of 19 patients with MGUS and 17 with smoldering multiple myeloma, mean duration of this disease was studied for 61 months +/- 50. Subjects were divided into two groups: the first was a 4g crossover group and the second was an 8g crossover group. Both doses were found to reduce serum light ratio, a marker that is used to determine disease progression; the higher the serum light ratio, the more

---

[38] Epelbaum R, et al. Nutrition and Cancer. 2010;62(8):1137

[39] He, Z-Y, et al. Cancer Investigation. 2011;29:208

progressive the disease. Curcumin was found to reduce the ratio, ultimately slowing down the progression of the disease, a highly significant result.[40]

Curcumin interactions

Curcumin has several interactions, most of which are theoretical and have not been demonstrated clinically. There is a possibility of interference with drugs metabolized through 3A4. Curcumin may also be altered by drugs that affect 1A1 or 2B1. Caution should also be used when administering curcumin with chemotherapeutics.[41, 42]

Milk thistle (*Silybum marianum*)

Milk thistle is an herb with a high concentration of bioflavonoids, including silymarin. Silybin is the most studied and potentially active. In this herb, flavonoids help prevent the carcinogenic pathway in a variety of ways.

Silybin inhibits the conversion of initiated cells to dormant tumor cells. This growth inhibition has been noted in human prostate, breast and cervical carcinoma cells. This effect is mediated via impairment of receptor and non-receptor tyrosine kinase signaling pathways along with inhibition of TNFα release and associated changes in cell cycle progression.[43, 44]

Growth factors: inhibition of EGFR

Silymarin (particularly silybin) inhibits receptor and non-receptor tyrosine kinase signaling pathways. It also inhibits TNF-α mRNA expression.[45] These actions result in decreased cell growth and reduced DNA synthesis in human prostate, breast and cervical carcinoma cells.

---

[40] Golombick T, et al. Am J Hematol. 2012;00:0000.
[41] Volak LP, et al. Drug Metab Dispos. 2008;36(8):1594
[42] Sen GS, et al. J Bio Chem. 2011;286:1
[43] Bhatia, et al. Cancer Lett, 1999
[44] Zi, et al. Biochem Biophys Res Commun, 1997
[45] Bhatia, Cancer Let, 1999

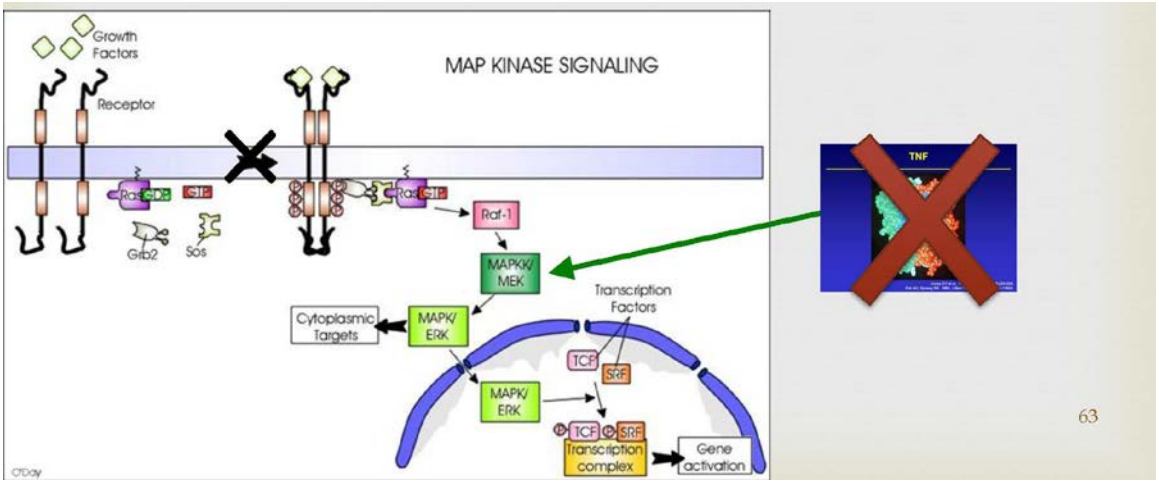


Figure 16

Prostate cancer

Milk thistle has been studied in vitro in prostate cancer, and has been shown to reduce inflammatory pathways in prostate cancer cells. Specifically, silymarin inhibits human prostate carcinoma DU145 cells, while silybin has been shown to target EGFR, IGF-1R, and NF-kappaB pathways in prostate carcinoma cells.[46, 47]

Apoptosis

Bladder transitional cancer cell lines treated with silybin have been shown to experience significant growth inhibition and apoptosis. These effects were due to activation of capase-3 and modulation of cyclin cascade.[48]

[46] Zi, et al. Cancer Res, 1998
[47] Singh and Agarwal, Mol Carcinog, 2006
[48] Tyagi, Carcinogenesis, Apr 2004

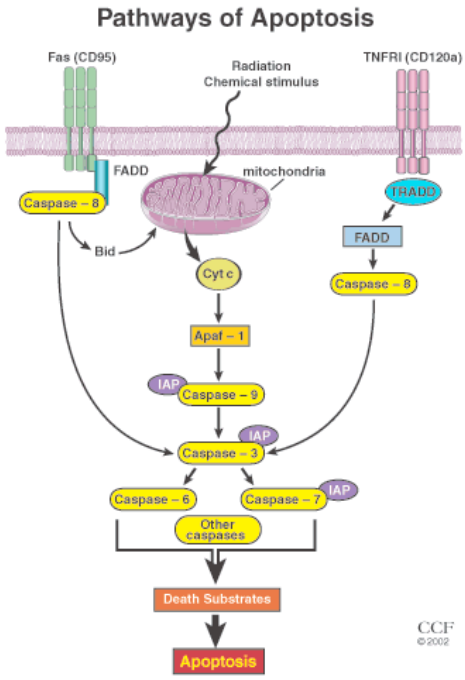


Figure 12

Pharmacology

Case studies have reviewed the pharmacological effects of milk thistle in prostate cancer. In one case study, six men with localized prostate cancer who were planned for prostatectomy received a fairly high dose of silybin-phytosome prior to surgery. Subjects had prostate tissue removed. Fairly low levels of penetration into the prostate tissue were found.[49]

Acute lymphoblastic leukemia (children)

Acute lymphoblastic leukemia, a disease that occurs in children, is very difficult to treat. Studies have shown that children with this disease who were give milk thistle versus placebo had significantly lower liver enzymes, much better toleration to chemotherapy, and were able to make it through chemotherapy.[50]

[49] Flaig TW, et al. Prostate. 2010;70(8):848
[50] Ladas E, et al. Cancer 2010;116:506

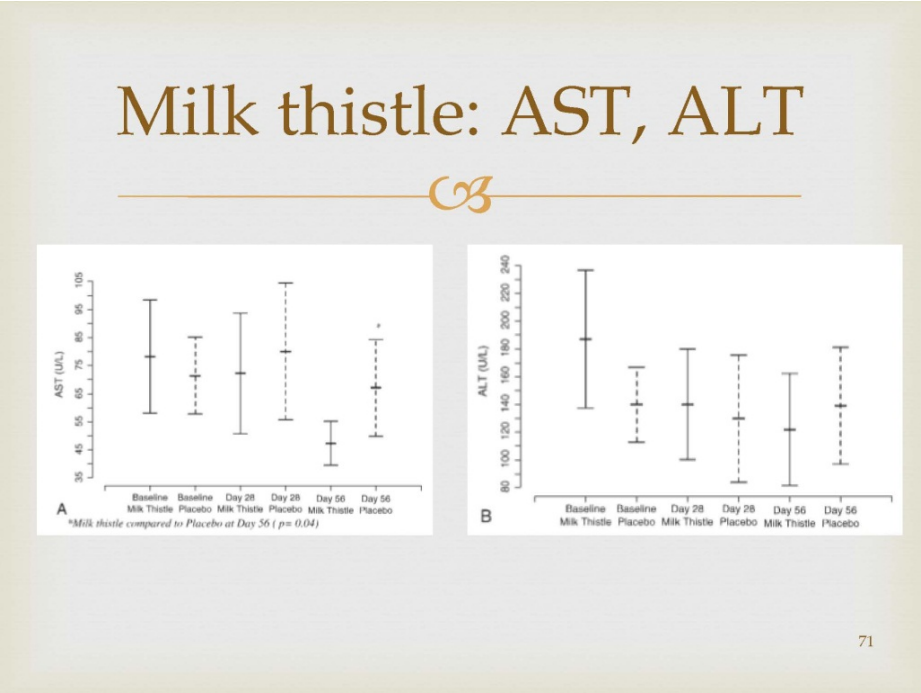


Figure 18

Hepatitis C

Milk thistle is extremely effective in the treatment of hepatitis C and hepatocellular carcinoma. Several trials have indicated the utility of milk thistle flavonoids in preventing the conversion of hepatitis into hepatocellular carcinoma, or lowering the risk.

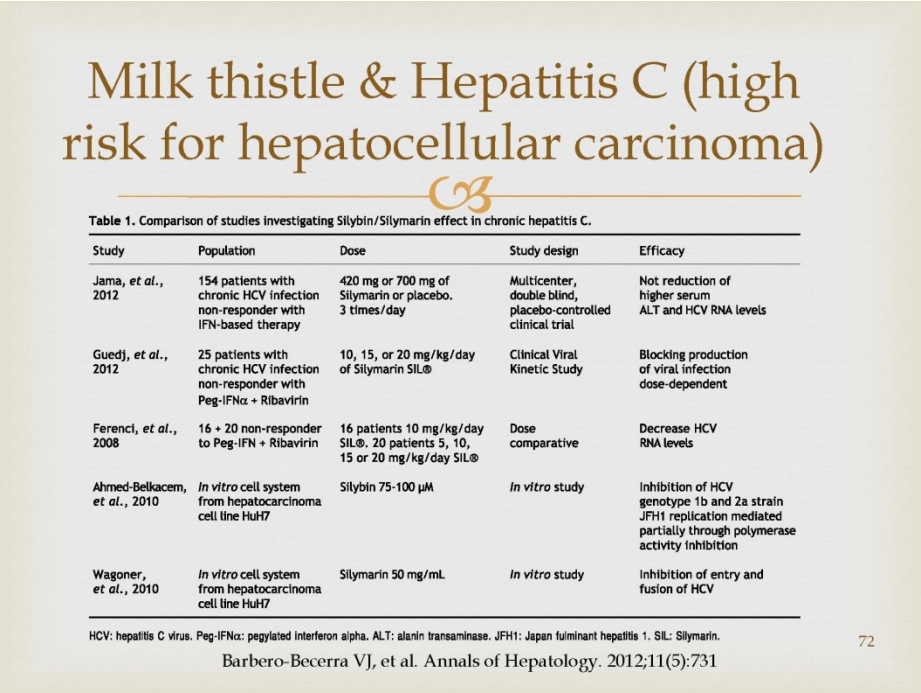


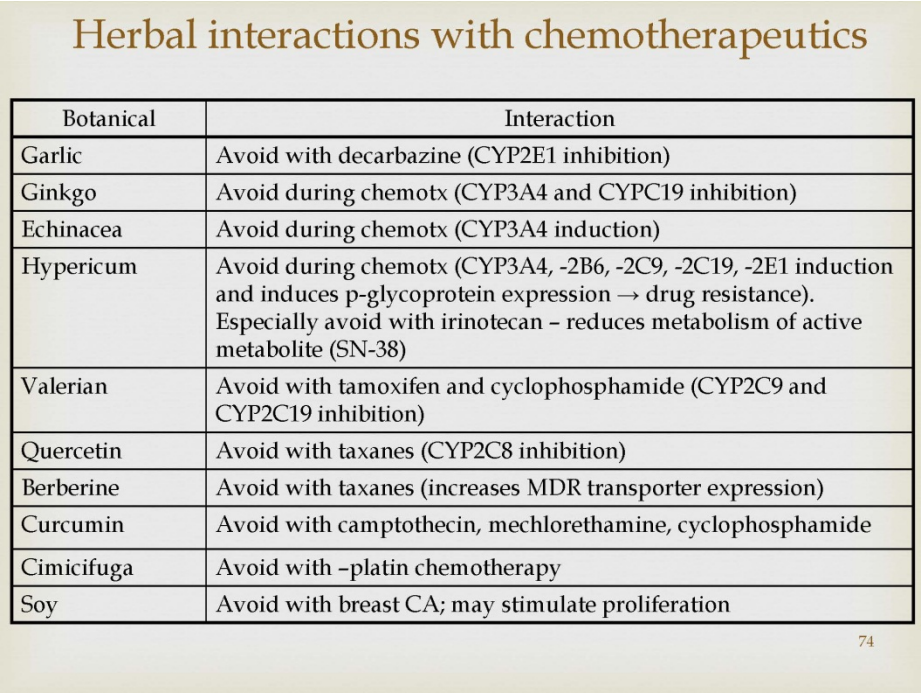
Figure 13

Drug interactions

In vivo studies suggest that silymarin may inactivate or modulate P450s 3A4 and 2C9; however, these effects have not been demonstrated in humans to alter the CYP3A4 substrate indinavir or other drugs usually metabolized by these P450s. For this reason, the data has questionable clinical relevance.

Herbal interactions with chemotherapeutics

In general, caution should be taken when using certain botanicals with chemotherapeutics as indicated in figure 20.



Herbal interactions with chemotherapeutics

Botanical	Interaction
Garlic	Avoid with decarbazine (CYP2E1 inhibition)
Ginkgo	Avoid during chemotx (CYP3A4 and CYPC19 inhibition)
Echinacea	Avoid during chemotx (CYP3A4 induction)
Hypericum	Avoid during chemotx (CYP3A4, -2B6, -2C9, -2C19, -2E1 induction and induces p-glycoprotein expression → drug resistance). Especially avoid with irinotecan – reduces metabolism of active metabolite (SN-38)
Valerian	Avoid with tamoxifen and cyclophosphamide (CYP2C9 and CYP2C19 inhibition)
Quercetin	Avoid with taxanes (CYP2C8 inhibition)
Berberine	Avoid with taxanes (increases MDR transporter expression)
Curcumin	Avoid with camptothecin, mechlorethamine, cyclophosphamide
Cimicifuga	Avoid with –platin chemotherapy
Soy	Avoid with breast CA; may stimulate proliferation

74

Figure 14

Conclusion

When someone is diagnosed with cancer, it affects their health on a variety of levels. Treating cancer is not just about averting the carcinogenic pathway for patients; treatment is comprised of many different levels of healing. This journey often involves becoming educated about optimal treatment plans, connecting with others and using complementary therapies to optimize physical well-being. Botanicals such as green tea, turmeric and milk thistle can be incredibly effective at treating and managing cancer. When used in conjunction with more traditional treatment options, botanicals have been shown to extend expected lifespan, increase traditional medication efficacy and minimize cancer recurrence. As the rate of cancer continues to increase, botanicals can be utilized to help diminish the damage of this rampantly spreading disease.

Contributor

Dr. Lise Alschuler is a naturopathic doctor with board certification in naturopathic oncology. She graduated from Brown University with an undergraduate degree in medical anthropology and received a doctoral degree in naturopathic medicine from Bastyr University in 1994. Dr. Alschuler is the Vice President of Quality and Education at Emerson Ecologics. She is past-President of the American Association of Naturopathic Physicians and was a founding board member of the Oncology Association of Naturopathic Physicians.

