Prostate Cancer, Nutrition, and Dietary Supplements (PDQ®)

Introduction

Men in the United States get prostate cancer more than any other type of cancer except skin cancer. It is found mainly in older men. In the United States, about one out of five men will be diagnosed with prostate cancer. Most men diagnosed with prostate cancer do not die of it.

Complementary and alternative medicine (CAM) is a form of treatment used in addition to (complementary) or instead of (alternative) standard treatments. CAM treatments generally are not considered standard medical approaches. Standard treatments go through a long and careful research process to prove they are safe and effective, but less is known about most types of CAM.

CAM use among prostate cancer patients is reported to be common. CAM treatments used by prostate cancer patients include certain foods, dietary supplements, herbs, vitamins, and minerals.

This PDQ CAM summary gives general information about using foods and dietary supplements to lower the risk of developing prostate cancer or for treating prostate cancer, its symptoms, or side effects of disease treatment. In addition, this summary has sections for several specific foods or dietary supplements:

- Calcium
- Green Tea
- Lycopene
- Modified Citrus Pectin
- Pomegranate
- Selenium
- Soy
- Vitamin D
- Vitamin E
• Combination Therapies

• Other Prostate Health Supplements

More topics will be added over time. These sections include the following information for each food or dietary supplement:

• How it is given or consumed.
• Reviews of laboratory and animal studies.
• Results of population studies and clinical trials.
• Side effects or risks.
• Food and Drug Administration (FDA) information.

Overview of CAM Use in Prostate Cancer

Studies of CAM use to treat prostate cancer have shown the following:

• Men who have prostate cancer are more likely to take dietary supplements than men who do not have prostate cancer.
• Prostate cancer patients with the healthiest eating habits (for example, eating lots of fish rich in omega-3 fatty acids and vegetables) are the most likely to take dietary supplements.
• Reasons given by prostate cancer patients for using CAM treatments include boosting the immune system, improving quality of life, and lowering the risk of the cancer coming back.

Studies of CAM use to lower the risk of developing prostate cancer or to prevent it from coming back have shown the following:

• A study of men with a family history of prostate cancer found that over half used vitamins or other dietary supplements, including those sold for prostate health or cancer prevention, such as some of those listed in this summary.
• A study of men at a prostate cancer screening clinic found that well over half took multivitamins and a smaller number took herbal supplements.
• A study of prostate cancer survivors found that up to one-third took vitamins or minerals.
• Although many prostate cancer patients use CAM therapies, only about half of them tell their doctors about their use of CAM.

Studies of why prostate cancer patients do or don’t decide to use CAM show that their choice is
based on many factors, including their medical history, their beliefs about the safety and side effects of CAM compared to standard treatments, and their need to feel in control of their treatment.

Questions and Answers About Calcium

1. **What is calcium?**

   Calcium is a mineral that is needed for basic blood vessel, muscle, and nerve functions, cell-to-cell signaling, and hormone release. It is the most common mineral in the body. The body stores calcium mainly in bone tissue. Calcium naturally occurs in some foods and is added to other foods. It is also available as a dietary supplement.

2. **How is calcium administered or consumed?**

   The main sources of calcium in the American diet are foods and dietary supplements. About one-third of dietary calcium comes from milk and milk products like cheese and yogurt. Vegetable sources include Chinese cabbage, kale, and broccoli. Spinach contains calcium but it is not in a form that is well absorbed by the body. Foods with calcium added include many fruit juices and drinks, tofu, and cereals.

   In the United States, almost half the population takes dietary supplements containing calcium. However, most research about calcium and prostate cancer risk has studied only calcium consumed in the diet and not calcium taken in supplements.

3. **Have any preclinical (laboratory or animal) studies been conducted using calcium?**

   Laboratory and animal research has been done to study the effects of calcium in prostate cancer.

   Studies of calcium in the laboratory have shown the following:

   • In a 2011 study, prostate cancer cells were treated with cow milk, almond milk, soy milk, casein, or lactose. Growth of prostate cancer cells (LNCaP) was stimulated when they were treated with cow milk. Treatment with soy milk did not affect the growth of prostate cancer cells, and treatment with almond milk treatment slowed the growth of prostate cancer cells.

   Studies of calcium in animal models of prostate cancer have shown the following:

   • Strains of mice which developed prostate cancer that acts like human cancer were fed low-calcium diets or high-calcium diets. Prostate cancer growth was found to be similar in mice fed either low- or high-calcium diets.
• Dietary vitamin D and calcium were studied in mice injected with prostate cancer cells and fed specific diets (including high-calcium plus vitamin D or normal calcium and no vitamin D). The mice that received the normal calcium and no vitamin D diet had more prostate cancer growth than mice fed the other diets.

4. Have any clinical trials (research studies with people) of calcium been conducted?

Studies of people in many parts of the world have been done to find out if there is a link between dairy products, calcium, and prostate cancer risk.

Population studies

Population studies look for risk factors and ways to control disease in large groups of people. Population studies of dairy products, dietary calcium, and prostate cancer risk have shown mixed results. These studies may be hard to interpret because other major nutrients in dairy products, such as fats, and factors such as age and body mass index have not been taken into account.

Overall, however, studies suggest that high total calcium intake may be linked with increased risk of advanced and metastatic prostate cancer compared with lower amounts of calcium. More studies are needed about the effects of calcium and/or dairy products on prostate cancer risk and how these effects develop in the body.

Clinical trial of preventing prostate cancer

In a randomized clinical trial reported in 2005, men were given calcium (1200 mg/day) or a placebo for 4 years and were followed up for 12 years. During the first 6 years of the study, there were markedly fewer cases of prostate cancer in the calcium group compared to the placebo group. After 10 years, however, there was no meaningful difference in the number of prostate cancers in the calcium group compared to the placebo group.

Reviews of many studies combined

Reviews of many studies combined showed mixed findings about whether consuming calcium and dairy products affects the risk of prostate cancer:

• A 2005 review of many studies found a possible link between an increased risk of prostate cancer and a diet high in dairy products and calcium. See the PDQ summary on Prostate Cancer Prevention for more information.

• A 2008 review of 45 observational studies found no link between consuming dairy products and the risk of prostate cancer.

• A review of cohort studies published between 1996 and 2006 found that consuming
milk and dairy products did increase the risk of prostate cancer.

- A 2013 review for the U.S. Preventive Services Task Force found that taking Vitamin D and/or calcium supplements showed no overall effect on rates of cancer or deaths from cancer, including prostate cancer.

5. **Is calcium approved by the U.S. Food and Drug Administration (FDA) for use as a cancer treatment in the United States?**

The U.S. Food and Drug Administration has not approved the use of calcium as a treatment for cancer or any other medical condition.

Calcium is available in the United States in food products and dietary supplements. Because dietary supplements are regulated as foods, not as drugs, FDA approval is not required unless specific claims about disease prevention or treatment are made.

### Current Clinical Trials

Check NCI’s list of cancer clinical trials for CAM clinical trials on [calcium carbonate for prostate cancer](#) and [calcium citrate for prostate cancer](#) that are actively enrolling patients.

General information about clinical trials is also available from the [NCI website](#).

### Questions and Answers About Green Tea

1. **What is green tea?**

   Tea has been consumed in Asia since ancient times. Sailors first brought tea to England in the 17th century. Other than water, tea is the most widely consumed beverage in the world. Tea comes from the *Camellia sinensis* plant. The way the leaves of this plant are processed determines the type of tea produced.

   Many of the possible health benefits studied in green tea are thought to be from compounds called polyphenols. Polyphenols are a large group of plant chemicals that include catechins (antioxidants that help protect cells from damage caused by free radicals).

   Catechins make up most of the polyphenols in green tea. The most active catechin in green tea is epigallocatechin-3-gallate (EGCG).

   To make green tea, the tea leaves are roasted in a wok (or, historically, steamed) to preserve the catechins and retain freshness. Black tea is made using a process that causes the catechins and other compounds in the leaves to oxidize, producing darker colored tea. Oolong tea is made from partially oxidized leaves.
Some studies suggest that green tea may protect against cardiovascular disease and some types of cancer, including prostate cancer. Clinical trials designed to study whether green tea is useful in treating prostate cancer are in the early stages. There is not enough evidence to show whether green tea is effective in treating prostate cancer.

2. **How is green tea administered or consumed?**

Green tea may be consumed as a beverage or taken in dietary supplements.

3. **Have any preclinical (laboratory or animal) studies been conducted using green tea?**

Laboratory and animal research has been done to study the effects of green tea in prostate cancer.

Studies of green tea in the laboratory have shown the following:

- EGCG was shown to block the stimulating effect of androgen (a male sex hormone) on human prostate tumor cells, slow their spread, and increase cell death.
- Prostate cancer cells were treated with either EGCG or EGCG-loaded nanoparticles. While both treatments decreased cell spread and increased cell death, the nanoparticle treatment was more effective at lower levels, suggesting this type of delivery system for EGCG may make it easier for the body to use and improve EGCG's anticancer activity.
- Green tea polyphenols may cause anticancer effects by blocking histone deacetylases (HDAC) which are found in large amounts in cancer cells, including those in prostate cancer. Treating prostate cancer cells with green tea polyphenols lowered HDAC activity and caused cell death.

Studies of green tea in animal models of prostate cancer have shown the following:

- Strains of mice created to develop prostate cancer that acts like human cancer were given either plain water or water treated with green tea catechins (comparable to a human drinking 6 cups of green tea/ day). After 24 weeks, the mice given plain water had developed prostate cancer while the mice given water with green tea catechins showed only prostatic intraepithelial neoplasia (PIN) lesions. The findings suggested that green tea catechins may help delay the development of prostate cancer by blocking a protein involved in cancer growth.
- In a study of EGCG, mice were implanted with prostate cancer cells and injected with EGCG or placebo 3 times/ week. The mice that received the EGCG treatment had lower levels of proteins needed for androgen activity than those treated with placebo. The findings suggested that EGCG blocks the stimulating effect of androgen on tumor cells
in a way that may be useful in prostate cancer that can be treated with hormone therapy and also in prostate cancer that does not respond to hormone therapy.

- In another study of EGCG, strains of mice created to develop prostate cancer that acts like human cancer were given EGCG in drinking water (comparable to a human drinking 6 cups of green tea/day) starting at either 12 weeks of age or 28 weeks of age. EGCG treatment prevented high-grade PIN lesions in mice that began treatment at 12 weeks but not in those that began treatment at 28 weeks of age.

- In a study of green tea polyphenols, these strains of mice were given polyphenols in drinking water starting at different ages (to match different stages of prostate cancer). All the green tea-fed mice were tumor-free longer than water-fed control mice, and the mice that were fed with green tea the earliest benefitted the most.

- In another study of green tea polyphenols, these strains of mice were fed polyphenols by mouth (comparable to a human drinking 6 cups of green tea/day). As measured by MRIs over time, tumor development was delayed and tumor growth was slowed in the polyphenol-fed mice compared to water-fed mice. In addition, the polyphenols caused high levels of cell death, possibly limiting the spread of cancer to distant parts of the body.

- Safety studies of Polyphenon E (a green tea extract with a mixture of catechins) have been done in dogs given various doses by mouth. Mixed findings of safety and harms in fasting dogs compared to fed dogs using different types of Polyphenon E are being reviewed.

4. **Have any clinical trials (research studies with people) of green tea been conducted?**

Population studies and clinical trials have been done to find out if green tea may be useful in preventing or treating prostate cancer.

**Population studies**

Population studies look for risk factors and ways to control disease in large groups of people. A review of many population studies combined, mainly from Asia, showed mixed findings about whether green tea had a protective effect or no effect on prostate cancer risk. Many factors may be involved in these mixed results, including study location, tobacco and alcohol use, and other dietary differences. Black tea was not found to affect prostate cancer risk. Overall, population studies suggest that green tea may help protect against prostate cancer in Asian populations. As more people drink green tea worldwide, including in the United States, further population studies will add to information about whether green tea or green
tea catechins may help protect against prostate cancer.

**Clinical trials of preventing prostate cancer**

A study assigned 60 men with high-grade prostatic intraepithelial neoplasia (HGPIN) to take green tea catechin capsules (600 mg / day) or a placebo. After 1 year, 9 men in the placebo group were diagnosed with prostate cancer compared to 1 man in the green tea catechin group. The findings suggest that green tea catechins may lower the risk of prostate cancer in patients at high risk for the disease. Two year follow-up showed that this effect was long-lasting. A larger, multicenter trial is underway.

**Clinical trials of treating prostate cancer**

Clinical trials designed to study whether green tea is useful in treating prostate cancer have shown the following:

Patients scheduled to undergo radical prostatectomy were assigned to drink green tea, black tea, or soda five times/day for 5 days. Bioavailable tea polyphenols were found in prostate tissue samples of patients who drank either green tea or black tea. In addition, prostate cancer cells treated with blood taken from patients after they drank tea grew and divided more slowly than cells treated with blood taken from patients before they drank tea.

Fifty patients scheduled to undergo radical prostatectomy were assigned to take Polyphenon E (800 mg EGCG) or a placebo daily for 3 to 6 weeks. Patients treated with Polyphenon E had lower blood levels of prostate specific antigen (PSA) and insulin-like growth factor -1 (a protein linked with increased risk of prostate cancer) than patients treated with placebo, but these differences were not meaningful. The findings suggest that the possible anticancer effects of green tea polyphenols may need to be studied in longer treatment trials.

Patients scheduled to undergo radical prostatectomy were assigned to drink either green tea, black tea, or water. In this study, men drinking green tea showed a decrease in PSA levels along with a decrease in NF-kappa B levels.

A small group of hormone-refractory prostate cancer patients were given capsules of green tea extract (375 mg of polyphenols/day) for up to 5 months. The study showed that the green tea treatment was well tolerated by most of the patients. However, no patient had a meaningful decrease in PSA levels and all 19 patients had disease progression within 1 to 5 months.

Patients with androgen-independent prostate cancer that had spread to other places in the body consumed powdered green tea extract (6 grams / day for up to 4 months). Of the forty-two participants, one had a meaningful decrease in blood PSA levels which did not last longer than 2 months. Green tea extract was well tolerated by most of the study patients. However,
there were 6 reports of serious side effects, including insomnia, confusion, and fatigue. The findings suggest that green tea extract may have limited benefits in patients with advanced prostate cancer.

5. **Have any side effects or risks been reported from green tea?**

Four phase I studies of Polyphenon E in single doses or multidoses were done in healthy volunteers. Polyphenon E was given in a range of doses and found to be well tolerated. Side effects were generally mild, with no serious side effects reported. The most frequently reported side effects thought to be related to the drug include headache, nausea, abdominal pain, diarrhea, upset stomach, dizziness, and weakness. Gastrointestinal side effects were usually mild, occurring most often in patients taking the drug on an empty stomach and at the highest doses.

The FDA Division of Drug Oncology Products recommends that Polyphenon E should be taken with food by patients in clinical trials and that liver function tests should be done during treatment.

Various types and doses of green tea extracts taken by mouth have been linked with several cases of liver damage in recent years. Most of those affected were women and many were taking green tea extract for weight loss. Most patients recovered within 4 months after stopping the green tea extract. However, there is one case report of acute liver failure in a woman who then needed a liver transplant. Her doctors concluded that her condition was likely caused by over-the-counter green tea extract capsules for weight loss.

Green tea has been well tolerated in clinical studies of patients with prostate cancer. One study found that the most commonly reported side effects of green tea were gastrointestinal symptoms. These were mild except for two reports of severe anorexia and moderate breathing problems.

6. **Is green tea approved by the U.S. Food and Drug Administration (FDA) for use as a cancer treatment in the United States?**

The U.S. Food and Drug Administration has not approved the use of green tea as a treatment for cancer or any other medical condition.

Green tea is available in the United States in food products and dietary supplements. Because dietary supplements are regulated as foods, not as drugs, FDA approval is not required unless specific claims about disease prevention or treatment are made.

**Current Clinical Trials**

Check NCI’s list of cancer clinical trials for CAM clinical trials on green tea for prostate cancer and
green tea extract for prostate cancer that are actively enrolling patients.

General information about clinical trials is also available from the NCI website.

Questions and Answers About Lycopene

1. What is lycopene?

   Lycopene is a carotenoid (a natural pigment made by plants). Lycopene protects plants from light-related stress and helps them use the energy of the sun to make nutrients. Lycopene is found in fruits and vegetables like tomatoes, apricots, guavas, and watermelons.

   The main source of lycopene in the American diet is tomato-based products. Lycopene is more bioavailable (easier for the body to use) in processed tomato products like tomato paste and tomato puree than in raw tomatoes.

   Eating carotenoids, including lycopene, along with dietary fat may help the body absorb them. For example, one study showed that more lycopene was absorbed from diced tomatoes cooked with olive oil than diced tomatoes cooked without olive oil.

   Lycopene in the diet may affect antioxidant activity and communication between cells. Laboratory and animal studies have shown that lycopene may help lower the risk of prostate, skin, breast, lung, and liver cancers. However, clinical trials of whether lycopene lowers cancer risk have shown mixed results.

2. How is lycopene administered or consumed?

   Lycopene may be consumed in the diet or taken in dietary supplements.

3. Have any preclinical (laboratory or animal) studies been conducted using lycopene?

   Laboratory research and animal studies have been done to find out if lycopene may be useful in preventing or treating prostate cancer.

   Studies of lycopene in the laboratory have shown the following:

   • Prostate cancer cells treated with lycopene had changes in their cell division cycle, leading to less cancer cell growth.

   • In prostate cancer cells treated with lycopene, cholesterol levels were lower, leading to less cancer cell growth & more cancer cell damage.

   • Treating prostate cancer cells with lycopene may change the way androgen (male hormone) is taken up and used in the cells, causing less cancer cell growth.

   • Combining lycopene with standard cancer drugs may help stop the spread of different
types of prostate cancer cells more than when drugs are used alone. Used together with a cancer drug, lycopene may block the way insulin-like growth factor (IGF) is taken up by the cells, causing less cancer cell spread.

Studies of animal models of prostate cancer treated with lycopene have shown the following:

- Strains of mice created to develop prostate cancer that acts like human cancer were fed a diet with either lycopene beadlets or tomato paste. Mice on the lycopene beadlet diet had a greater decrease in prostate cancer rates than mice on the tomato paste diet. This suggests that lycopene might have more cancer protective effects than tomato paste.
- Combining lycopene with a substance found in dried tomatoes (FruHis) slowed the growth of prostate cancer cells in rats more than either lycopene or FruHis alone.
- A study of mice injected with human prostate cancer cells showed that mice treated with either lycopene or beta carotene supplements had less tumor growth.
- A study of mice injected with human prostate cancer cells and treated with a certain chemotherapy drug, lycopene, or both showed that those treated with chemotherapy and lycopene lived longer and had smaller tumors than those treated with chemotherapy alone.

4. **Have any population studies or clinical trials (research studies with people) of lycopene been conducted?**

Several population studies and clinical trials have been done to find out if lycopene may be useful in preventing or treating prostate cancer.

**Population studies**

Population studies look for risk factors and ways to control disease in large groups of people. Population studies of prostate cancer risk have shown the following mixed results:

- Population studies in men have found that high amounts of lycopene in the diet are linked with a lower risk of developing prostate cancer.
- Some studies have shown that lycopene levels in the blood and tissue of patients with cancer are lower than in those who do not have cancer. However, other studies have not shown this.
- A 2013 review of several studies combined found that men who ate large amounts of raw or cooked tomatoes may have a slightly lower risk of prostate cancer.
- A study found no link between lycopene and tomatoes in the diet and prostate cancer risk.
risk in the overall population. However, in men with a family history of the disease, higher amounts of lycopene in the diet were linked with a lower risk of prostate cancer. Another study in the same group of men found no difference in blood levels of lycopene between healthy men and men who developed prostate cancer.

Many issues may be involved in these mixed findings, including sources and types of lycopene, other dietary differences, obesity, tobacco and alcohol use, and genetic risk factors.

**Clinical trials of preventing prostate cancer**

Clinical trials designed to study whether lycopene is useful in preventing prostate cancer have shown the following:

- Men with benign prostate hyperplasia (BPH) or prostate cancer were given tomato sauce dishes for 3 weeks before scheduled surgery to remove the prostate. The study found that they had markedly lower prostate specific antigen (PSA) levels and more cancer cell death found in the prostate when examined after surgery than a similar group of patients who did not receive the tomato sauce dishes.

- Men with high-grade prostatic intraepithelial neoplasia (HGPIN) who took lycopene supplements for 2 years had a greater decrease in PSA levels and fewer cases of prostate cancer than those who did not. This indicated that lycopene may be useful in preventing HGPIN from developing into prostate cancer. In another study of men at high risk of prostate cancer (such as men with HGPIN), those who took a daily multivitamin with no lycopene and those who took the same multivitamin plus lycopene (30 mg/day) for 4 months showed no difference in PSA levels.

**Clinical trials of treating prostate cancer**

Clinical trials designed to study whether lycopene is useful in treating prostate cancer have shown the following:

- Men with prostate cancer that had not spread were given lycopene supplements (30mg/day) for 3 weeks before surgery to remove the prostate. Those who received lycopene supplements had smaller tumors and lower PSA levels than those who did not. This study suggests that lycopene may be helpful in treating prostate cancer. Another study of men with prostate cancer that had not spread showed that men who took lycopene supplements (10mg/day for 1 year) had lower PSA velocity (a measure of how fast PSA levels in the blood increase over time) after treatment.

- Men who had biochemical relapse of prostate cancer (a rise in the blood level of PSA after treatment with surgery or radiation) were given different doses of lycopene
supplements (ranging from 15 mg/day to 120 mg/day) for 1 year. Study results showed that lycopene seemed safe & had no side effects, but did not change PSA levels in biochemically relapsed prostate cancer.

- Men with hormone-refractory prostate cancer (HRPC) (tumors that do not respond to treatment with hormones) were given lycopene supplements for periods of 3 or 6 months in 2 different studies. These studies showed mixed results in lowering PSA levels in men with HRPC.
- Men with androgen-independent prostate cancer (tumors that do not need androgen to grow) consumed lycopene in either tomato paste or tomato juice daily for 4 months. Study results showed that lycopene may not be effective in lowering PSA levels in androgen-independent cancer.

5. **Have any side effects or risks been reported from lycopene?**

Lycopene has been consumed by prostate cancer patients with very few side effects in many clinical trials. Doses ranging from 10 to 120 mg/day have caused only occasional gastrointestinal symptoms (e.g. diarrhea, nausea and vomiting, bloating, gassiness and stomach irritation). In one study, symptoms went away when lycopene was taken with meals.

6. **Is lycopene approved by the U.S. Food and Drug Administration (FDA) for use to prevent or treat cancer in the United States?**

The U.S. Food and Drug Administration has not approved the use of lycopene as a treatment for cancer or any other medical condition.

Lycopene is available in the United States in food products and dietary supplements. Because dietary supplements are regulated as foods, not as drugs, FDA approval is not required unless specific claims about disease prevention or treatment are made. An FDA review in 2007 found that there was not enough evidence to allow a claim that lycopene helps lower cancer risk.

**Current Clinical Trials**

Check NCI’s list of cancer clinical trials for CAM clinical trials on lycopene for prostate cancer that are actively enrolling patients.

General information about clinical trials is also available from the NCI website.

**Questions and Answers About Modified Citrus**
Pectin

1. What is modified citrus pectin?

Pectin is a type of polysaccharide (a carbohydrate with many small sugar molecules that are chemically linked). Pectin is found in the cell walls of most plants and has gel-like qualities that are useful in making many types of food and medicine.

Citrus pectin is found in the peel and pulp of citrus fruits such as oranges, grapefruit, lemons, and limes. Citrus pectin can be modified with high pH and heat to break its molecules into smaller pieces. Modified citrus pectin (also called MCP) can be digested and absorbed by the body.

2. How is MCP administered or consumed?

MCP may be taken by mouth in powder or capsule form.

3. Have any preclinical (laboratory or animal) studies been conducted using MCP?

A study in prostate cancer cells compared 3 different kinds of pectin: citrus pectin, PectaSol (a dietary supplement with MCP), and fractionated pectin powder. Prostate cancer cells treated with the pectin powder had more damage than those treated with citrus pectin or PectaSol. However, when citrus pectin was modified by heating it, it caused the same amount of damage to prostate cancer cells as the pectin powder.

Only a few studies have reported the effects of MCP in animal models of cancer, including one prostate cancer study. Rats injected with prostate cancer cells and treated with MCP showed less spread of the cancer to the lungs but no effect on tumor growth at the original cancer site.

4. Have any population studies or clinical trials (research studies with people) of MCP been conducted?

A few studies in prostate cancer patients suggest that MCP may have some anticancer benefits.

In a study of patients with advanced solid tumors, including prostate cancers, MCP powder in water was given 3 times/day for at least 8 weeks. The study showed some quality of life improvements in physical functioning, overall health, fatigue, pain, and insomnia. About one-fourth of patients showed stable disease after 8 weeks of treatment and a smaller number had stable disease for more than 24 weeks. Since the study did not include a group of patients who did not receive MCP for comparison, it was not designed to be able to tell if any of these changes were due to the addition of MCP. The primary goal of the study was to determine if MCP would be well tolerated by cancer patients, and it was.
In a study of the effect of MCP on prostate-specific antigen (PSA) doubling time (how long it takes PSA levels in the blood to increase by 100 percent), prostate cancer patients who had rising PSA levels were given 6 PectaSol capsules 3 times/day for 12 months. After treatment, 7 out of 10 patients showed a slowing of PSA doubling time.

5. **Have any side effects or risks been reported from MCP?**

Two studies of MCP showed that most patients had very few side effects. Itching, stomach upset, and gassiness were reported in one study. In another study, 3 patients had abdominal cramps and diarrhea that went away when their treatment was stopped.

6. **Is MCP approved by the U.S. Food and Drug Administration (FDA) for use to prevent or treat cancer in the United States?**

The U.S. Food and Drug Administration has not approved the use of MCP as a treatment for cancer or any other medical condition.

MCP is available in the United States in food products and dietary supplements. Because dietary supplements are regulated as foods, not as drugs, FDA approval is not required unless specific claims about disease prevention or treatment are made.

**Current Clinical Trials**

Check NCI’s list of cancer clinical trials for CAM clinical trials on modified citrus pectin for prostate cancer that are actively enrolling patients.

General information about clinical trials is also available from the NCI website.

**Questions and Answers About Pomegranate**

1. **What is pomegranate?**

The pomegranate fruit (*Punica granatum* L.) is native to Asia and grown throughout the Mediterranean, Southeast Asia, East Indies, Africa, and the United States. Pomegranate has been used for medicinal purposes since ancient times.

Different parts of the pomegranate fruit have bioactive compounds (chemicals found in small amounts that have actions in the body that may promote good health). These include:

- The peel, which makes up half the fruit and contains bioactive compounds such as phenolics, flavonoids, and ellagitannins (the main source of antioxidant activity);

- The seeds, which contain punicic acid, an omega-5 fatty acid; and
The aril (outer layer surrounding the seeds), which contains phenolics and flavonoids including anthocyanins, which give the pomegranate fruit and juice their red color.

2. **How is pomegranate administered or consumed?**

Pomegranate may be consumed in the diet or taken in dietary supplements.

3. **Have any preclinical (laboratory or animal) studies been conducted using pomegranate?**

Laboratory studies of pomegranate in cancer cell lines include the following:

- A study of 13 pomegranate compounds showed some were able to slow the growth and spread of prostate cancer cells and to cause cell death. Higher doses were found to be more effective. Punicic acid (a bioactive compound found in pomegranate seeds) was shown to have the strongest effect in causing cell death.

- Three types of prostate cancer cell lines were treated with either pomegranate extract, pomegranate juice, or two of their bioactive compounds. All pomegranate treatments were shown to increase cell death and decrease the spread of cancer cells, with higher doses found to be more effective. In the cell line that was dependent on androgen (male hormone) for growth, all treatments affected the way androgen was taken up and used.

- Other studies in cancer cell lines found that the anticancer activity of pomegranate included effects on certain enzymes and pathways involved in cancer, such as the insulin-like growth factor (IGF) system.

Studies of animal models of prostate cancer in which the animals were given pomegranate have shown the following:

- A study of mice injected with prostate tumor-forming cells found that mice that drank pomegranate extract in water had tumors that were smaller and took longer to develop than tumors in mice that drank normal water.

- In a study of strains of mice created to develop prostate cancer that acts like human cancer, all mice that were given normal water for 28 weeks developed tumors. Only one-fifth to one-third of the mice that received pomegranate extract in water developed tumors, with the mice that received the highest amounts of pomegranate extract having the fewest tumors.

4. **Have any clinical trials (research studies with people) of pomegranate been conducted?**

Two clinical trials that studied pomegranate in prostate cancer patients have been fully
reported.
In a study of 48 patients with rising prostate-specific antigen (PSA) levels after surgery or radiation therapy, patients were given 8 ounces of pomegranate juice daily for up to 33 months. Drinking pomegranate juice was related to a slowing of PSA doubling time (how long it takes PSA levels in the blood to increase by 100 percent). In addition, when prostate cancer cells (LNCaP) in the lab were treated with study patients’ blood before and after the study, there was a decrease in cell growth and increase in cell death following pomegranate treatment.
In a phase II study of patients with rising PSA levels after therapy for localized prostate cancer, patients were given 1 gram or 3 gram doses of pomegranate extract. Both doses of pomegranate extract were related to a slowing of PSA doubling time with no adverse effects.

5. **Have any side effects or risks been reported from pomegranate?**

Two studies of pomegranate juice in either prostate cancer patients or patients with erectile dysfunction reported no serious side effects.

6. **Is there any reason people should avoid pomegranate juice?**

Some pomegranate products may contain added sugar. Certain groups, such as the American Institute for Cancer Research (AICR), recommend avoiding sugary drinks. For more information, see the AICR website.

7. **Is pomegranate approved by the U.S. Food and Drug Administration (FDA) for use to prevent or treat cancer in the United States?**

The U.S. Food and Drug Administration has not approved the use of pomegranate as a treatment for cancer or any other medical condition.

Pomegranate is available in the United States in food products and dietary supplements. Because dietary supplements are regulated as foods, not as drugs, FDA approval is not required unless specific claims about disease prevention or treatment are made.

**Current Clinical Trials**

Check NCI’s list of cancer clinical trials for CAM clinical trials on pomegranate-extract pill for prostate cancer, pomegranate juice for prostate cancer, and pomegranate liquid extract for prostate cancer that are actively enrolling patients.

General information about clinical trials is also available from the NCI website.
Questions and Answers About Selenium

1. **What is selenium?**

Selenium is a trace mineral (a nutrient that is essential to humans in tiny amounts). Selenium is found in certain proteins that are active in many body functions, including reproduction and immunity. Food sources of selenium include meat, vegetables, and nuts. The amount of selenium found in the food depends on the selenium content of the soil where the food grows. Selenium is stored in the thyroid gland, liver, pancreas, pituitary gland, and kidneys.

Selenium is found in an enzyme called glutathione peroxidase which acts as an antioxidant. However, in high amounts, selenium may act as a pro-oxidant (a substance that can make oxygen byproducts that may damage cells).

Selenium may play a role in many diseases, including cancer. Animal and population studies have suggested that supplementing the diet with selenium may lower the risk of cancer. Results from the Nutritional Prevention of Cancer Trial (NPC) showed that, although selenium supplements did not affect the risk of skin cancer, they markedly lowered the rates of lung, colorectal, and prostate cancer. However, studies of how selenium levels in the blood affect the risk of developing of prostate cancer have shown mixed results.

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) was begun by the National Institutes of Health in 2001 to study the effects of selenium and/or vitamin E on the development of prostate cancer.

2. **How is selenium administered or consumed?**

Selenium may be consumed in the diet or taken in dietary supplements. For adults, the recommended daily allowance for selenium is 55 µg/day.

3. **Have any preclinical (laboratory or animal) studies been conducted using selenium?**

Laboratory studies to find out if selenium may be useful in preventing or treating prostate cancer have shown the following:

- Different forms of selenium have been shown to slow the growth and spread of prostate cancer cells.
- Selenium nanoparticles may be less toxic to normal tissues than other selenium compounds.

Studies of selenium in animal models of prostate cancer have shown the following:

- A study in mice looked at the effect of dietary selenium on prostate cancer prevention starting at different ages. Adult mice and younger mice were fed selenium-enriched
diets or diets with no selenium for 6 months or 4 weeks and then injected with human prostate cancer cells. Adult mice with selenium in their diets developed fewer tumors than adult mice with diets lacking in selenium. However, in younger mice, dietary selenium had no effect on tumor development.

- Strains of mice which developed prostate cancer that acts like human cancer were treated with 2 forms of selenium, MSeA and methylselenocysteine (MSeC), or water only. In the selenium-treated mice, growth of precancerous lesions was slowed and cancer cell death was increased compared to the water-treated mice. MSeA treatment also increased survival time of the study mice. The mice that received MSeA treatment starting at 10 weeks of age had less aggressive prostate cancer than did mice starting treatment at 16 weeks of age, suggesting early treatment with MSeA may be more effective than later treatment.

4. **Have any population studies or clinical trials (research studies with people) of selenium been conducted?**

Population studies and clinical trials have been done to find out if selenium may be useful in preventing or treating prostate cancer.

**Population studies**

Population studies look for risk factors and ways to control disease in large groups of people. Studies of how selenium levels in the blood affect the risk of developing of prostate cancer have shown mixed results. One study tracking subjects for up to 10 years found that men with higher levels of selenium in their blood had a lower risk of prostate cancer. Another study found that prostate cancer patients had lower whole blood selenium levels than did healthy men. However, a 2009 study of prostate cancer patients found that men with higher selenium levels in their blood were at greater risk of being diagnosed with aggressive prostate cancer. These differences may be due to genetic variations among individual patients.

**Clinical trials of preventing/ treating prostate cancer**

Clinical trials of the effects of selenium on prostate specific antigen (PSA) levels or the development of prostate cancer have shown mixed results, including the following:

- In a study reported in 2013, men at high risk for prostate cancer were given either daily doses of high-selenium yeast (200 µg or 400 µg) or a placebo for up to 5 years. There were no differences in prostate cancer rates or PSA velocity in men who took the selenium supplement compared to those who took the placebo.
In an earlier study, men with high-grade prostatic intraepithelial neoplasia (HGPIN) were given either a selenium supplement (200 µg/ day) or a placebo for 3 years or until they were diagnosed with prostate cancer. The results suggested that selenium supplements had no effect on prostate cancer risk.

Sixty men were given either a selenium glycinate supplement (200 µg/ day) or a placebo for 6 weeks. Blood samples were collected at the start and the end of the study. Compared to the placebo group, men who received selenium supplements showed higher activity of two selenium enzymes in their blood and lower levels of PSA at the end of the study.

The Health Professionals Follow-Up Study included 4,459 men diagnosed with prostate cancer that had not spread. The study found that taking selenium supplements (140 or more µg/ day) after diagnosis may increase the risk of death from prostate cancer and recommended that men with prostate cancer use caution in taking selenium supplements.

The Selenium and Vitamin E Cancer Prevention Trial (SELECT)

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) was a large clinical trial begun by the National Institutes of Health in 2001 to study the effects of selenium and/or vitamin E on the development of prostate cancer. Over 35,000 men, aged 50 years and older, were randomly assigned to receive one of the following combinations daily for 7-12 years:

- Vitamin E (alpha-tocopherol acetate, 400 IU / day) and a placebo;
- Selenium (L-selenomethionine, 200 mcg/ day) and a placebo;
- Vitamin E and selenium; or
- Two placebos.

First results of SELECT reported in 2009 found no meaningful difference in the rate of prostate cancer among the 4 groups. In the Vitamin E alone group, there was a slight increase in the rate of prostate cancer and in the selenium alone group, there was a slight increase in the rate of diabetes. Even though these changes were not clearly shown to be due to the supplement, the men in the study were advised to stop taking the study supplements.

Updated results of SELECT in 2011 showed that selenium supplements had no meaningful effect on prostate cancer risk; however, men taking vitamin E alone had a 17% increase in prostate cancer risk compared to men in the placebo group.

In 2014, further results of SELECT showed that selenium supplements in men with low selenium levels at the start of the trial had no effect on prostate cancer risk; however,
selenium supplements in men who had high levels of selenium at the start of the trial increased the risk of high-grade prostate cancer.

Several factors may have affected study results, including the dose of vitamin E chosen and the form of selenium used.

5. **Have any side effects or risks been reported from selenium?**

Selenium supplements were well tolerated in many clinical trials. In two published trials, there were no differences reported in adverse effects between placebo or treatment groups. However, in the SELECT trial, selenium supplements were linked with a slight increase in the rate of diabetes mellitus.

6. **Is selenium approved by the U.S. Food and Drug Administration (FDA) for use as a cancer treatment in the United States?**

The U.S. Food and Drug Administration has not approved the use of selenium supplements for the treatment or prevention of cancer or any other medical condition.

Selenium is available in the United States in food products and dietary supplements. Because dietary supplements are regulated as foods, not as drugs, FDA approval is not required unless specific claims about disease prevention or treatment are made.

**Current Clinical Trials**

Check NCI’s list of cancer clinical trials for CAM clinical trials on [selenium for prostate cancer](http://www.cancer.gov/about-cancer/treatment/cam/patient/prostate-supplements-pdq#section/all) that are actively enrolling patients.

General information about clinical trials is also available from the [NCI website](http://www.cancer.gov/about-cancer/treatment/cam/patient/prostate-supplements-pdq#section/all).

**Questions and Answers About Soy**

1. **What is soy?**

The soybean plant has been grown in Asia for food since ancient times. Soy first arrived in Europe and North America in the 18th century. The soybean can be processed into a wide variety of products including soy milk, miso, tofu, soy flour, and oil.

Soy foods contain many phytochemicals that may have health benefits. Isoflavones are the most widely researched compounds in soy. Major isoflavones in the soybean include genistein (which may be the most bioactive isoflavone), daidzein, and glycinein. Isoflavones protect the soybean plant from stress and have antioxidant, antimicrobial, and antifungal actions.
Isoflavones are phytoestrogens (estrogen-like substances found in plants) that attach to estrogen receptors in cells. Genistein has been shown to affect many pathways in prostate cancer cells involved in the growth and spread of cancer.

2. **How is soy administered or consumed?**

Soy may be consumed in the diet or taken in dietary supplements.

3. **Have any preclinical (laboratory or animal) studies been conducted using soy?**

Laboratory research and animal studies have been done to find out if soy may be useful in preventing or treating prostate cancer.

Studies of soy in the laboratory have shown the following:

- Several laboratory studies have found that treating human prostate cancer cells with isoflavones (such as genistein or daidzein) interferes with pathways in prostate cancer cells related to inflammation and cancer growth and spread.

- Some laboratory studies have found that treating prostate cancer cells with whole soy extract (containing all the major isoflavones) or combining other plant-based compounds with isoflavones may have more anticancer effects than using single isoflavones. One study compared treating human prostate cancer cells with soy isoflavones, curcumin (a yellow pigment of the spice turmeric that is being studied in cancer prevention), or a combination of the two compounds. Results showed that combining curcumin and isoflavones was more effective in lowering prostate-specific antigen (PSA) levels than using either compound alone.

Studies of animal models of prostate cancer treated with soy have shown the following mixed results:

- Strains of mice created to develop prostate cancer that acts like human cancer were fed a diet with genistein or a control diet. Compared with mice on the control diet, the mice fed the genistein diet had less prostate cancer cell growth and lower levels of growth promoting proteins.

- A study of mice that were genetically modified to produce prostate cancer found that mice fed a low-dose genistein diet had more spread of cancer than mice fed either a high-dose genistein diet or a diet with no genistein. This suggests that the effects of genistein on prostate cancer may vary depending on dose and on how early it is given.

- A study in mice implanted with advanced human prostate cancer found that those given daily genistein in peanut oil developed more tumors in other parts of the body than mice given peanut oil without genistein.
• In a study of combining radiation therapy with soy isoflavones, mice implanted with prostate cancer cells were treated with genistein, mixed isoflavones (genistein, daidzein, and glycine), and/or radiation. Mixed isoflavones were found to be more effective than genistein in slowing prostate tumor growth. Combining mixed isoflavones with radiation was found to be most effective in slowing tumor growth.

4. Have any population studies or clinical trials (research studies with people) of soy been conducted?

Many population studies and clinical trials have been done to find out if soy may be useful in preventing or treating prostate cancer. Soy products studied include dietary supplements, drinks, and bread.

Population studies

Population studies look for risk factors and ways to control disease in large groups of people. Population studies of soy intake and prostate cancer risk have shown the following mixed results:

• A 2009 review of many studies combined showed that men eating large amounts of nonfermented soy foods (for example, tofu and soybean milk) had a lower risk of prostate cancer. Eating large amounts of fermented foods (for example, miso) was not found to affect the risk of prostate cancer.

• A 2013 review showed that PSA levels and sex hormone levels were not markedly different in men treated with soy, compared with men who were not treated with soy.

Clinical trials of preventing prostate cancer

• In a study of Japanese men who underwent a prostate biopsy but who did not have cancer, some received a daily supplement of soy isoflavones (40 mg) and curcumin (100 mg), while others received a placebo. After 6 months, there were no differences in PSA levels between the supplement group and the placebo group overall. However, among patients with higher PSA levels at the start, those who received the supplement had meaningful decreases in PSA levels compared to patients in the placebo group.

• A study was done to find out if a soy diet standard in Asia would be practical for European men to follow. Healthy men ate either a high-soy (2 daily soy servings) or low-soy (usual) diet for 3 months, then crossed over to the other diet. Lower PSA levels were seen with the high-soy diet. Results showed that study volunteers were able to follow the high-soy diet.
Men at risk for prostate cancer or with low-grade prostate cancer were given either soy protein, alcohol-washed soy protein (which is lower in isoflavones), or milk protein (which has no isoflavones) for 6 months. PSA levels did not differ among the groups at 3 months or 6 months. Fewer cases of prostate cancer were found after 6 months in men who consumed either type of soy protein than in men who consumed milk protein.

Clinical trials of treating prostate cancer

• In a trial of soy isoflavones, prostate cancer patients with rising PSA levels who had been treated with radiation therapy consumed a soy drink daily for 6 months. The soy drink contained 65-90 mg of isoflavones. Results showed that the soy drink had very few side effects and slowed PSA doubling time (how long it takes PSA levels in the blood to increase by 100 percent). These findings indicate that consuming the soy drink may have helped slow the progression of prostate cancer.

• In a trial of genistein (a major isoflavone), prostate cancer patients scheduled for radical prostatectomy received either a placebo or genistein (30 mg/day) for 3-6 weeks before surgery. PSA levels in patients who received genistein decreased slightly while PSA levels in those who received the placebo increased slightly.

• In a trial of soy isoflavone, prostate cancer patients scheduled for prostatectomy received either capsules (containing 80 mg/day of isoflavones) or a placebo for up to 6 weeks before surgery. There was no difference in PSA, testosterone, or cholesterol level changes between the two groups.

• A trial of a soy protein supplement (containing 60 mg/day of isoflavones) studied patients with early-stage prostate cancer. Those who received the supplement for 12 weeks had slightly greater decreases in PSA and testosterone levels than those who received placebo.

• Trials of whole soy were done in men scheduled for surgery to remove the prostate. In one study, patients given soy supplements for 2 weeks before surgery showed much higher levels of isoflavones in prostate tissue than in blood. In another study, patients who ate high-phytoestrogen bread (containing soy or soy and linseed) had greater decreases in PSA levels than those who ate wheat bread.

• Two trials of a soy isoflavone supplement were done in prostate cancer patients receiving antiandrogen therapy. Side effects of antiandrogen therapy may include sexual dysfunction, lower quality of life, and changes in mental functioning. In both studies, men who received the isoflavone supplement (160 mg/day) for 12 weeks
showed no improvement in side effects of antiandrogen therapy compared to men who received a placebo.

5. **Have any side effects or risks been reported from soy?**

Soy products and isoflavones have been consumed by prostate cancer patients with very few side effects in many clinical trials. The most commonly reported side effects were minor gastrointestinal symptoms.

6. **Is soy approved by the U.S. Food and Drug Administration (FDA) for use to prevent or treat cancer in the United States?**

The U.S. Food and Drug Administration has not approved the use of soy as a treatment for cancer or any other medical condition.

Soy is available in the United States in food products and dietary supplements. Because dietary supplements are regulated as foods, not as drugs, FDA approval is not required unless specific claims about disease prevention or treatment are made.

**Current Clinical Trials**

Check NCI’s list of cancer clinical trials for CAM clinical trials on soy isoflavones for prostate cancer and soy protein isolate for prostate cancer that are actively enrolling patients.

General information about clinical trials is also available from the NCI website.

**Questions and Answers About Vitamin D**

1. **What is vitamin D?**

Vitamin D (also called calcipotriol, cholecalciferol, or ergocalciferol) is a fat-soluble vitamin found in enriched dairy products, fatty fish, fish liver oil, and eggs.

Vitamin D has many actions in the body including:

- Helping absorb calcium from food in the small intestine.
- Improving muscle strength and immune system function.
- Lowering inflammation.
- Maintaining levels of calcium and phosphate in the blood.

Vitamin D is needed for bone growth and protects against osteoporosis in adults. Vitamin D level is usually checked by measuring the amount of 25-hydroxyvitamin D in the blood.
2. **What are the sources of vitamin D?**

Vitamin D is made naturally by the body when exposed to sunlight. Vitamin D may also be consumed in the diet or taken in dietary supplements.

3. **Have any preclinical (laboratory or animal) studies been conducted using vitamin D?**

Laboratory and animal research studies suggest that vitamin D may have effects on prostate cancer cells through various pathways.

Preclinical studies of vitamin D in prostate cancer have shown the following:

- A study of a form of vitamin D showed that it may prevent prostate cancer cells from sticking to endothelium, the thin layer of cells that lines the inside of blood vessels, lymph vessels, and body cavities.

- In a 2011 study, mice were fed a diet with adequate vitamin D or a diet lacking vitamin D and were then injected with prostate cancer cells into bone marrow or into soft tissues. The mice lacking vitamin D developed bone tumors that were larger and grew faster than the mice that had adequate levels of vitamin D. However, there was no difference in soft tissue tumors among mice with different vitamin D levels. Results of this study show that a lack of vitamin D is linked with growth of prostate cancer cells in bone but not in soft tissue.

- A study of vitamin D as adjuvant therapy (therapy to make other types of treatment more effective) combined it with cryotherapy (freezing). Mice injected with prostate cancer cells were treated with calcitriol with or without cryotherapy. Those who were treated with the combination of calcitriol and freezing had more cancer cell death and less cancer cell spread than those who were treated with either calcitriol alone or freezing alone.

4. **Have any population studies or clinical trials (research studies with people) of vitamin D been conducted?**

Many population studies and clinical trials have been done to find out if vitamin D may be useful in preventing or treating prostate cancer.

**Population studies**

Population studies look for risk factors and ways to control disease in large groups of people. Population studies of vitamin D and prostate cancer risk have shown the following mixed results:

- Vitamin D levels in patients with prostate cancer that had not spread were taken annually for 5 years. Throughout the course of the study, lack of vitamin D was a
common finding among these patients.

- Another study in patients with prostate cancer suggested that medium or high levels of vitamin D in the blood may be linked with better outcomes than lower levels. These findings indicate that vitamin D levels may play a role in whether or not the disease will worsen and may be a factor in predicting outcome in prostate cancer patients.

- One thousand patients with prostate cancer and 1000 control patients in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study were followed for up to 20 years. Results suggested that men with higher blood levels of vitamin D had a greater risk of developing prostate cancer than men with lower vitamin D levels.

- In a case-cohort analysis from the Selenium and Vitamin E Cancer Prevention Trial (SELECT), men who had moderate blood levels of vitamin D (45–70 nmol/L) were found to have a markedly lower risk of aggressive prostate cancer than men who had either lower or higher levels of vitamin D.

- Vitamin D from sunlight exposure has been studied for possible effects on prostate cancer rates. A 2006 study found that PSA levels rise at a slower rate during the spring and summer compared to other times of the year, suggesting this may be due to higher vitamin D levels during those months. Another study found that while men with low levels of sun exposure had increased risk of all prostate cancers, those with prostate cancer who had less sun exposure showed lower risk of advanced disease.

- Geographic patterns of deaths in the United States from 1950 to 1994 showed that higher death rates from prostate cancer occurred in parts of the country with lower levels of UV radiation from sunlight. This effect is strongest in places more than 40 degrees north of the equator, where sunlight is weakest during the winter months. These findings support the theory that lack of vitamin D increases the risk for prostate cancer.

**Reviews of many population studies combined**

A 2008 review of 45 observational studies combined found no link between intake of vitamin D and prostate cancer risk.

A 2011 review of 25 studies combined found no link between either vitamin D in the diet or blood levels of vitamin D and the risk of prostate cancer.

A 2014 review of 21 studies combined found that high levels of vitamin D in the blood may be linked with a higher risk of prostate cancer. Many factors may affect these findings, since some studies propose men from higher income groups may have higher vitamin D levels and are more likely to get PSA testing, leading to higher rates of reported prostate cancer.
Clinical trials of treating prostate cancer

Clinical trials in patients with prostate cancer have shown the following:

• A clinical trial treated patients with prostate cancer that had recurred (come back) with calcitriol (the active form of vitamin D) and naproxen for 1 year. Results showed that the combination of calcitriol and naproxen was effective in slowing the rate of rising PSA levels in study patients, suggesting it may slow disease progression.

• In a 2010 study, patients with prostate cancer that did not respond to hormone therapy were treated with calcitriol and dexamethasone. The results indicated that while the treatment was well tolerated, it did not have an effect on PSA levels in the study patients.

• In a 2009 study, patients with locally advanced or metastatic prostate cancer were treated with vitamin D. The study reported that one in every 5 patients who took vitamin D had improved PSA levels, suggesting that vitamin D may be an effective therapy for patients with advanced prostate cancer.

5. Is vitamin D approved by the U.S. Food and Drug Administration (FDA) for use as a cancer treatment in the United States?

The U.S. Food and Drug Administration has not approved the use of vitamin D as a treatment for cancer or any other medical condition.

Vitamin D is available in the United States in food products and dietary supplements. Because dietary supplements are regulated as foods, not as drugs, FDA approval is not required unless specific claims about disease prevention or treatment are made.

Current Clinical Trials

Check NCI ’s list of cancer clinical trials for CAM clinical trials on vitamin D for prostate cancer that are actively enrolling patients.

General information about clinical trials is also available from the NCI website.

Questions and Answers About Vitamin E

1. What is vitamin E?

Vitamin E is a nutrient that may protect against chronic diseases such as cardiovascular disease. Vitamin E is being studied in the prevention of some types of cancer.
There are eight different forms of vitamin E: four tocopherols (alpha-, beta-, gamma-, and sigma-) and four tocotrienols (alpha-, beta-, gamma-, and sigma-). Compared with other tocopherols, alpha-tocopherol (the form of vitamin E commonly found in dietary supplements) is found in greater amounts in the body and is the most active. Most vitamin E in the diet comes from gamma-tocopherol. Food sources of vitamin E include vegetable oils, nuts, and egg yolks.

Many of the possible health benefits of Vitamin E may be from its antioxidant activity. Vitamin E is a powerful antioxidant that protects cell membranes from damage caused by free radicals. Vitamin E also has other functions involved in cell signaling pathways and gene expression.

2. **How is vitamin E administered or consumed?**

Vitamin E may be consumed in the diet or taken in dietary supplements.

3. **Have any clinical trials (research studies with people) of vitamin E been conducted?**

Population studies and clinical trials have been done to find out if vitamin E may be useful in preventing or treating prostate cancer.

**Population studies**

Population studies look for risk factors and ways to control disease in large groups of people. Population studies of vitamin E in prostate cancer risk have shown the following:

- The NIH -AARP Diet and Healthy Study studied whether vitamin E in supplements and in the diet of volunteers may prevent prostate cancer. After 5 years, no link between vitamin E supplements and prostate cancer risk was found. However, a lower risk of advanced prostate cancer was found in those who had high intakes of one form of vitamin E (gamma-tocopherol).

- In a 2010 study that measured blood levels of trace elements and vitamin E, those who had prostate cancer had markedly lower blood levels of vitamin E than those who did not have prostate cancer. In addition, those who had higher PSA levels had lower levels of vitamin E in their blood.

- Blood levels of alpha-tocopherol and gamma-tocopherol and prostate cancer risk were studied in participants in the Prostate, Lung, Colorectal and Ovarian (PLCO) Screening Trial. Men with higher levels of alpha-tocopherol had lower rates of prostate cancer, but this was noted only in current smokers and those who had recently quit.

- In a review of many studies combined involving 370,000 men from several countries, higher blood levels of alpha-tocopherol were linked with a lower risk of prostate
cancer in all patients, not just smokers.

Clinical trials of preventing or treating prostate cancer

- In the Physicians’ Health Study II, men received either vitamin E supplements (400 IU synthetic alpha-tocopherol taken every other day) and/or vitamin C supplements (500 mg synthetic ascorbic acid taken daily) and were followed for an average of 8 years. The overall rates of prostate cancer were very similar in the men who received vitamin E supplements and in those who did not, suggesting that vitamin E may not prevent prostate cancer. Furthermore, vitamin E did not have an effect on total cancer or death rates in these participants.

- The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study (ATBC) trial measured blood levels of alpha-tocopherol and dietary intake of vitamin E in men who were followed for up to 19 years. Findings showed no link between vitamin E in the diet and prostate cancer risk, but showed that higher levels of alpha-tocopherol in the blood may be linked with a lower risk for developing advanced prostate cancer.

- Men in the ATBC trial who developed prostate cancer were studied to find out if serum alpha-tocopherol levels affected survival time. Higher serum alpha-tocopherol levels, at both time of diagnosis and at the 3-year time point, were linked with improved prostate cancer survival.

- A 2011 study of men who took part in The Carotene and Retinol Efficacy Trial (CARET) found that, among those who were current smokers, higher levels of serum alpha-tocopherols and gamma-tocopherols were linked with lower risk of aggressive prostate cancer.

The Selenium and Vitamin E Cancer Prevention Trial (SELECT)

The Selenium and Vitamin E Cancer Prevention Trial (SELECT) was a large clinical trial begun by the National Institutes of Health in 2001 to study the effects of selenium and/or vitamin E on the development of prostate cancer. Over 35,000 men, aged 50 years and older, were randomly assigned to receive one of the following combinations daily for 7-12 years:

- Vitamin E (alpha-tocopherol acetate, 400 IU/ day) and a placebo;
- Selenium (L-selenomethionine, 200 mcg/ day) and a placebo;
- Vitamin E and selenium; or
- Two placebos.

First SELECT results reported in 2009 found no meaningful differences in rates of prostate
cancer among the 4 groups. In the Vitamin E alone group, there was a slight increase in the rate of prostate cancer and in the selenium alone group, there was a slight increase in the rate of diabetes. Based on those findings, the men in the study were advised to stop taking the study supplements.

Updated SELECT results in 2011 showed that selenium supplements had no meaningful effect on prostate cancer risk; however, men taking vitamin E alone had a 17% increase in prostate cancer risk compared to men in the placebo group.

In 2014, further SELECT results showed that vitamin E supplements alone had no effect on prostate cancer risk in men with high levels of selenium at the start of the trial; however, vitamin E supplements increased the risk of low-grade and high-grade prostate cancer in men with lower levels of selenium at the start of the trial.

Several factors may have affected study results, including the dose of vitamin E chosen and the form of selenium used.

4. Have any side effects or risks been reported from vitamin E?

Alpha-tocopherols are deemed Generally Recognized as Safe by the U.S. Food and Drug Administration.

In the Physicians’ Health Study II, there were no marked differences in rates of gastrointestinal symptoms, fatigue, drowsiness, skin discoloration or rashes, or migraine between men who took vitamin E (400 IU every other day of alpha-tocopherol) and those who took a placebo. However, there was a higher number of hemorrhagic strokes in men who took vitamin E than in men who took a placebo. In the Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group, there was also an increase in hemorrhagic strokes among men in the group that took vitamin E (50 mg/day of alpha-tocopherol).

Earlier results from the SELECT trial showed no marked differences in rates of less severe adverse effects (such as hair loss, inflamed skin, and nausea) in the groups that took vitamin E (400 IU/day of all-rac-alpha-tocopherol) compared to the other treatment groups. Later follow-up of SELECT participants showed an increased risk of prostate cancer among men in the vitamin E alone group.

5. Is vitamin E approved by the U.S. Food and Drug Administration (FDA) for use as a cancer treatment in the United States?

The U.S. Food and Drug Administration has not approved the use of vitamin E as a treatment for cancer or any other medical condition.

Vitamin E is available in the United States in food products and dietary supplements. Because dietary supplements are regulated as foods, not as drugs, FDA approval is not required.
unless specific claims about disease prevention or treatment are made.

Current Clinical Trials

Check NCI ’s list of cancer clinical trials for CAM clinical trials on vitamin E for prostate cancer that are actively enrolling patients.

General information about clinical trials is also available from the NCI website.

Combination Therapies

Pomegranate, Green Tea, Broccoli, and Turmeric

Polyphenols are compounds found in many plants and give some flowers, fruits, and vegetables their color. Polyphenols have antioxidant activity that helps protect cells from damage caused by free radicals.

A food supplement high in polyphenols was studied in a group of men who had prostate cancer that had not spread. This supplement contained a combination of the following:

- Pomegranate whole fruit powder.
- Broccoli powder.
- Turmeric powder.
- Green tea extract.

In a randomized clinical trial, 199 men were given either the food supplement or a placebo for 6 months. Before the study began, slightly less than half of the men had rising prostate-specific antigen (PSA) levels after being treated with local therapy, and slightly more than half of the men were on active surveillance (not yet treated). In the group that took the supplement, median PSA levels rose much less than in the group that took the placebo. The food supplement was well tolerated and there were no marked differences reported in adverse effects between supplement and placebo groups. However, patients in the supplement group were more likely to have gastrointestinal symptoms (i.e., more gas and loose bowels).

Questions and Answers About Zyflamend

1. What is Zyflamend?

   Zyflamend is a dietary supplement that contains extracts of 10 different herbs:
• Rosemary.
• Turmeric.
• Ginger.
• Holy basil.
• Green tea.
• Hu zhang (*Polygonum cuspidatum*).
• Chinese goldthread.
• Barberry.
• Oregano.
• Baikal skullcap.

The extracts found in Zyflamend have anti-inflammatory activity and possible anticancer benefits. There is limited evidence about how Zyflamend may act against tumor growth. Zyflamend has been shown to interfere with the activity of COX-1 and COX-2 enzymes, which are involved in the development of inflammation and possibly cancer. Zyflamend may also act against the NF-kappa B and lipoxygenase (LOX) families of proteins that stimulate tumor growth.

2. **How is Zyflamend administered or consumed?**

   Zyflamend is taken as a dietary supplement in capsule form.

3. **Have any preclinical (laboratory or animal) studies been conducted using Zyflamend?**

   Laboratory and animal research has recently been done to study the effects of Zyflamend in cancer.

   Studies of Zyflamend in the laboratory have shown the following:

   • Human prostate cancer cells treated with different doses of Zyflamend had lower androgen (male hormone) receptor and prostate-specific antigen (PSA) levels compared with cells treated with a control substance; higher doses of Zyflamend were found to be more effective. Prostate cancer cells treated with both Zyflamend and bicalutamide (a nonsteroidal antiandrogen drug) showed lower levels of cell growth, PSA, and cancer survival proteins than prostate cancer cells treated with Zyflamend or bicalutamide alone.

   • A study in human prostate cancer cells found that a higher concentration of Zyflamend blocked both COX-1 and COX-2 activity; a lower concentration of Zyflamend
blocked COX-2 activity but had less effect on COX-1. Zyflamend was also found to limit the growth of prostate cancer cells. However, the prostate cancer cells in the study did not have high levels of COX-2, suggesting that Zyflamend may have effects on prostate cancer cells that are not related to COX activity.

- Prostate cancer cells were treated with insulin-like growth factor -1 (IGF-1, a protein linked with increased risk of prostate cancer) alone or together with Zyflamend. Cells treated with IGF-1 alone grew and spread more, while cells treated with both IGF-1 and Zyflamend grew and spread less. Zyflamend was also shown to decrease levels of the IGF-1 receptor and androgen receptor in prostate cancer cells.

Studies of Zyflamend in animal models of cancer have shown the following:

- Mice implanted with pancreatic tumor cells received either Zyflamend or a control treatment. The mice treated with Zyflamend showed lower levels of cancer survival proteins and higher levels of anticancer activity than mice in the control group.
- Mice implanted with pancreatic tumor cells received either Zyflamend, gemcitabine, or both. Tumor cells from mice that received the combination of Zyflamend and gemcitabine showed a much greater decrease in tumor growth than tumor cells from mice that received Zyflamend or gemcitabine alone. The findings suggested that Zyflamend may have made the pancreatic tumors more sensitive to treatment with gemcitabine.

4. **Have any clinical trials (research studies with people) of Zyflamend been conducted?**

A report of one patient with high-grade prostatic intraepithelial neoplasia (HGPIN) who received Zyflamend 3 times/day for 18 months showed that PSA levels were not affected. However, at the end of 18 months of treatment, repeat biopsies of the prostate did not show HGPIN or cancer.

In a phase I safety study of Zyflamend, patients with HGPIN took Zyflamend (780 mg) 3 times/day for 18 months with additional dietary supplements (probiotic supplement, multivitamin, green and white tea extract, Baikal skullcap, docosahexaenoic acid, holy basil, and turmeric). Zyflamend and the added dietary supplements were well tolerated and there were no serious side effects. At the end of 18 months of treatment, more than half of patients had benign biopsy results, about one-fourth had HGPIN, and about one in 8 had prostate cancer.

5. **Have any side effects or risks been reported from Zyflamend?**

A phase I safety study of Zyflamend (described above) reported no toxicity or serious side
effects. Some of the patients had mild heartburn that went away when Zyflamend was taken with food.

6. **Is Zyflamend approved by the U.S. Food and Drug Administration (FDA) for use as a cancer treatment in the United States?**

The U.S. Food and Drug Administration has not approved the use of Zyflamend as a treatment for cancer or any other medical condition.

Zyflamend is available in the United States as a dietary supplement. Because dietary supplements are regulated as foods, not as drugs, FDA approval is not required unless specific claims about disease prevention or treatment are made.

**Other Prostate Health Supplements**

**Overview**

Many widely available dietary supplements are marketed to support prostate health. African Cherry (*pygeum africanum*) and beta-sitosterol are two related supplements that have been studied as possible prostate cancer treatments.

**African Cherry / P. africanum**

African cherry or *Pygeum africanum* is a tree that grows in tropical climates. It is found in a number of African countries including Kenya, Madagascar, Uganda, and Nigeria. Bark from the *P. africanum* tree was used by African tribes to relieve urinary symptoms and stomach pain. In the 18th century, European travelers learned from South African tribes that *P. africanum* could treat bladder discomfort and “old man’s disease” (enlarged prostate).

Since 1969, bark extracts from *P. africanum* have been available as prescription drugs in Europe and have been widely used to treat benign prostatic hyperplasia (BPH). The bark contains a number of compounds including fatty acids and phytosterols (e.g., beta-sitosterol). The bark is processed and purified as an extract.

Laboratory studies and animal studies have shown that two substances in bark extract from *P. africanum* are active in blocking cells from taking up androgen. The antiandrogen activity found in *P. africanum* is at a markedly lower concentration than the antiandrogen activity found in flutamide (an anticancer drug).

**Beta-Sitosterol**
Beta-sitosterol is a member of the phytosterol family of phytochemicals and is widely found in plant life in different amounts. It is found in African cherry (*Pygeum africanum*), saw palmetto (*Serenoa repens*), and various nuts, beans, and seeds. It is one of several phytosterols (plant sterols) that have a chemical structure similar to cholesterol. Phytosterols, including beta-sitosterol, limit the amount of cholesterol that can be absorbed from the diet and they are being studied for their potential to protect against cardiovascular disease. Beta-sitosterol is very poorly absorbed by the body.

Studies suggest that phytosterols may have anticancer activity, but their exact actions are unknown. Phytosterols may affect immune and hormonal systems or may directly target cell cycles and cause cell death in tumors.

Laboratory studies have shown that high concentrations of beta-sitosterol markedly slow the growth of human prostate cancer cells and cause cancer cell death.

**Changes to This Summary (07/17/2015)**

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

Editorial changes were made to this summary.

**About This PDQ Summary**

**About PDQ**

Physician Data Query (PDQ) is the National Cancer Institute's (NCI's) comprehensive cancer information database. The PDQ database contains summaries of the latest published information on cancer prevention, detection, genetics, treatment, supportive care, and complementary and alternative medicine. Most summaries come in two versions. The health professional versions have detailed information written in technical language. The patient versions are written in easy-to-understand, nontechnical language. Both versions have cancer information that is accurate and up to date and most versions are also available in Spanish.

PDQ is a service of the NCI. The NCI is part of the National Institutes of Health (NIH). NIH is the federal government’s center of biomedical research. The PDQ summaries are based on an independent review of the medical literature. They are not policy statements of the NCI or the NIH.
Purpose of This Summary

This PDQ cancer information summary has current information about the use of nutrition and dietary supplements for reducing the risk of developing prostate cancer or for treating prostate cancer. It is meant to inform and help patients, families, and caregivers. It does not give formal guidelines or recommendations for making decisions about health care.

Reviewers and Updates

Editorial Boards write the PDQ cancer information summaries and keep them up to date. These Boards are made up of experts in cancer treatment and other specialties related to cancer. The summaries are reviewed regularly and changes are made when there is new information. The date on each summary ("Date Last Modified") is the date of the most recent change.

The information in this patient summary was taken from the health professional version, which is reviewed regularly and updated as needed, by the PDQ Cancer Complementary and Alternative Medicine Editorial Board.

Clinical Trial Information

A clinical trial is a study to answer a scientific question, such as whether one treatment is better than another. Trials are based on past studies and what has been learned in the laboratory. Each trial answers certain scientific questions in order to find new and better ways to help cancer patients. During treatment clinical trials, information is collected about the effects of a new treatment and how well it works. If a clinical trial shows that a new treatment is better than one currently being used, the new treatment may become "standard." Patients may want to think about taking part in a clinical trial. Some clinical trials are open only to patients who have not started treatment.

Clinical trials are listed in PDQ and can be found online at NCI's Web site. Many cancer doctors who take part in clinical trials are also listed in PDQ. For more information, call the Cancer Information Service 1-800-4-CANCER (1-800-422-6237).

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Disclaimer

The information in these summaries should not be used to make decisions about insurance reimbursement. More information on insurance coverage is available on Cancer.gov on the Managing Cancer Care page.

Contact Us

More information about contacting us or receiving help with the Cancer.gov Web site can be found on our Contact Us for Help page. Questions can also be submitted to Cancer.gov through the Web site’s E-mail Us.

General CAM Information

Complementary and alternative medicine (CAM)—also referred to as integrative medicine—includes a broad range of healing philosophies, approaches, and therapies. A therapy is generally called complementary when it is used in addition to conventional treatments; it is often called alternative when it is used instead of conventional treatment. (Conventional treatments are those that are widely accepted and practiced by the mainstream medical community.) Depending on how they are used, some therapies can be considered either complementary or alternative. Complementary and alternative therapies are used in an effort to prevent illness, reduce stress, prevent or reduce side effects and symptoms, or control or cure disease.

Unlike conventional treatments for cancer, complementary and alternative therapies are often
not covered by insurance companies. Patients should check with their insurance provider to find out about coverage for complementary and alternative therapies.

Cancer patients considering complementary and alternative therapies should discuss this decision with their doctor, nurse, or pharmacist as they would any therapeutic approach, because some complementary and alternative therapies may interfere with their standard treatment or may be harmful when used with conventional treatment.

Evaluation of CAM Approaches

It is important that the same rigorous scientific evaluation used to assess conventional approaches be used to evaluate CAM therapies. The National Cancer Institute and the National Center for Complementary and Integrative Health (NCCIH) are sponsoring a number of clinical trials (research studies) at medical centers to evaluate CAM therapies for cancer.

Conventional approaches to cancer treatment have generally been studied for safety and effectiveness through a rigorous scientific process that includes clinical trials with large numbers of patients. Less is known about the safety and effectiveness of complementary and alternative methods. Few CAM therapies have undergone rigorous evaluation. A small number of CAM therapies originally considered to be purely alternative approaches are finding a place in cancer treatment—not as cures, but as complementary therapies that may help patients feel better and recover faster. One example is acupuncture. According to a panel of experts at a National Institutes of Health (NIH) in November 1997, acupuncture has been found to be effective in the management of chemotherapy-associated nausea and vomiting and in controlling pain associated with surgery. In contrast, some approaches, such as the use of laetrile, have been studied and found ineffective or potentially harmful.

The NCI Best Case Series Program which was started in 1991, is one way CAM approaches that are being used in practice are being investigated. The program is overseen by the NCI’s Office of Cancer Complementary and Alternative Medicine (OCCAM). Health care professionals who offer alternative cancer therapies submit their patients’ medical records and related materials to OCCAM. OCCAM conducts a critical review of the materials and develops follow-up research strategies for approaches deemed to warrant NCI-initiated research.

Questions to Ask Your Health Care Provider About CAM

When considering complementary and alternative therapies, patients should ask their health care
provider the following questions:

- What side effects can be expected?
- What are the risks associated with this therapy?
- Do the known benefits outweigh the risks?
- What benefits can be expected from this therapy?
- Will the therapy interfere with conventional treatment?
- Is this therapy part of a clinical trial?
- If so, who is sponsoring the trial?
- Will the therapy be covered by health insurance?

To Learn More About CAM

National Center for Complementary and Integrative Health (NCCIH)

The National Center for Complementary and Integrative Health (NCCIH) at the National Institutes of Health (NIH) facilitates research and evaluation of complementary and alternative practices, and provides information about a variety of approaches to health professionals and the public.

NCCIH Clearinghouse

Post Office Box 7923 Gaithersburg, MD 20898–7923
TTY (for deaf and hard of hearing callers): 1–866–464–3615
Fax: 1–866–464–3616
E-mail: info@nccih.nih.gov
Web site: https://nccih.nih.gov/

CAM on PubMed

NCCAM and the NIH National Library of Medicine (NLM) jointly developed CAM on PubMed, a free and easy-to-use search tool for finding CAM-related journal citations. As a subset of the NLM’s PubMed bibliographic database, CAM on PubMed features more than 230,000 references and abstracts for CAM-related articles from scientific journals. This database also provides links to the Web sites of over 1,800 journals, allowing users to view full-text articles. (A subscription or other fee may be required to access full-text articles.) CAM on PubMed is available through the NCCIH Web site. It can also be accessed through NLM PubMed bibliographic database by selecting the
"Limits" tab and choosing "Complementary Medicine" as a subset.

Office of Cancer Complementary and Alternative Medicine

The NCI Office of Cancer Complementary and Alternative Medicine (OCCAM) coordinates the activities of the NCI in the area of complementary and alternative medicine (CAM). OCCAM supports CAM cancer research and provides information about cancer-related CAM to health providers and the general public via the NCI Web site.

National Cancer Institute (NCI) Cancer Information Service

U.S. residents may call the NCI Cancer Information Service toll free at 1-800-4-CANCER (1-800-422-6237) Monday through Friday from 8:00 am to 8:00 pm. A trained Cancer Information Specialist is available to answer your questions.

Food and Drug Administration

The Food and Drug Administration (FDA) regulates drugs and medical devices to ensure that they are safe and effective.

   Food and Drug Administration
   5600 Fishers Lane
   Rockville, MD 20857
   Telephone: 1–888–463–6332 (toll free)
   Web site: http://www.fda.gov/

Federal Trade Commission

The Federal Trade Commission (FTC) enforces consumer protection laws. Publications available from the FTC include:

   • Who Cares: Sources of Information About Health Care Products and Services
   • Fraudulent Health Claims: Don't Be Fooled

   Consumer Response Center
   Federal Trade Commission
   CRC-240
   Washington, DC 20580
   Telephone: 1-877-FTC-HELP (1-877-382-4357) (toll free)
   TTY (for deaf and hearing impaired callers): 202-326-2502
High-Dose Vitamin C–for health professionals (PDQ®)

Overview

This complementary and alternative medicine (CAM) information summary provides an overview of the use of high-dose vitamin C (also known as ascorbate or L-ascorbic acid) as a treatment for people with cancer. This summary includes a brief history of early clinical trials of high-dose vitamin C; reviews of laboratory, animal, and human studies; and current clinical trials.

This summary contains the following key information:

- Vitamin C is an essential nutrient with redox functions at normal physiologic concentrations.
- High-dose vitamin C has been studied as a treatment for cancer patients since the 1970s.
- Laboratory studies have reported that high-dose vitamin C has redox properties and decreased cell proliferation in prostate, pancreatic, hepatocellular, colon, mesothelioma, and neuroblastoma cell lines.
- Two studies of high-dose vitamin C in cancer patients reported improved quality of life and decreases in cancer-related side effects.
- Studies of vitamin C combined with other drugs in animal models have shown mixed results.
- Intravenous vitamin C has been generally well tolerated in clinical trials.

Many of the medical and scientific terms used in this summary are hypertext linked (at first use in each section) to the NCI Dictionary of Cancer Terms, which is oriented toward nonexperts. When a linked term is clicked, a definition will appear in a separate window.

Reference citations in some PDQ CAM information summaries may include links to external Web sites that are operated by individuals or organizations for the purpose of marketing or advocating the use of specific treatments or products. These reference citations are included for informational purposes only. Their inclusion should not be viewed as an endorsement of the content of the Web sites, or of any treatment or product, by the PDQ Cancer CAM Editorial Board or the National Cancer Institute.
General Information

Vitamin C is an essential nutrient that has redox functions, is a cofactor for several enzymes, and plays an important role in the synthesis of collagen.[1] A severe deficiency in vitamin C results in scurvy, which is associated with malaise, lethargy, easy bruising, and spontaneous bleeding.[2] One of the effects of scurvy is a change in collagen structure to a thinner consistency. Normal consistency is achieved with administration of vitamin C.

In the mid-20th century, a study hypothesized that cancer may be related to changes in connective tissue, which may be a consequence of vitamin C deficiency.[3] A review of evidence published in 1974 suggested that high-dose ascorbic acid may increase host resistance and be a potential cancer therapy.[4]

Vitamin C is synthesized from D-glucose or D-galactose by many plants and animals. However, humans lack the enzyme L-gulonolactone oxidase required for ascorbic acid synthesis and must obtain vitamin C through food or supplements.[1]

References


History

The earliest experience of using high-dose vitamin C (intravenous [IV] and oral) for cancer treatment was by a Scottish surgeon, Ewan Cameron, and his colleague, Allan Campbell, in the 1970s.[1] This work led to a collaboration between Cameron and the Nobel Prize–winning chemist Linus Pauling, further promoting the potential of vitamin C therapy in cancer management.[2,3] As a result, two clinical trials of oral vitamin C were conducted in the late 1970s and early 1980s. [4,5]

(Refer to the Human Studies section of this summary for more information about these early
Pharmacokinetic studies later revealed substantial differences in the maximum achieved blood concentrations of vitamin C based on the route of administration. When vitamin C is taken orally, plasma concentrations of the vitamin are tightly controlled, with a peak achievable concentration less than 300 µM. However, this tight control is bypassed with IV administration of the vitamin, resulting in very high levels of vitamin C plasma concentration (i.e., levels up to 20 mM).[6,7] Further research suggests that pharmacologic concentrations of ascorbate, such as those achieved with IV administration, may result in cell death in many cancer cell lines.[8]

Health care practitioners attending complementary and alternative medicine conferences in 2006 and 2008 were surveyed about usage of high-dose IV vitamin C in patients. Of the 199 total respondents, 172 had administered vitamin C to patients. In general, IV vitamin C was commonly used to treat infections, cancer, and fatigue.[9]

References

8. Verrax J, Calderon PB: Pharmacologic concentrations of ascorbate are achieved by parenteral


Laboratory/Animal/Preclinical Studies

In Vitro Studies

Numerous studies have demonstrated that pharmacological doses of ascorbic acid (0.1–100 mM) decrease cell proliferation in a variety of cancer cell lines.[1-5] Specifically, decreases in cell proliferation after ascorbic acid treatment have been reported for prostate,[6] pancreatic,[7,8] hepatocellular,[9] colon,[10] mesothelioma,[11] and neuroblastoma [12] cell lines.

The potential mechanisms through which treatment with high-dose ascorbic acid may exert its effects on cancer cells have been extensively investigated. Several studies have demonstrated that the in vitro direct cytotoxic effect of ascorbic acid on various types of cancer cells is mediated through a chemical reaction that generates hydrogen peroxide.[1,7,13,14] Treating colon cancer cells with 2 mM to 3 mM of ascorbic acid resulted in downregulation of specificity protein (Sp) transcription factors and Sp-regulated genes involved in cancer progression.[10] One study suggested that ascorbate-mediated prostate cancer cell death may occur through activation of an autophagy pathway.[6]

Differences in chemosensitivity to ascorbate treatment in breast cancer cell lines may depend on expression of the sodium-dependent vitamin C transporter 2 (SVCT-2).[15]

Research has suggested that pharmacological doses of ascorbic acid enhance the effects of arsenic trioxide on ovarian cancer cells,[16] gemcitabine on pancreatic cancer cells,[8] and combination treatment of gemcitabine and epigallocatechin-3-gallate (EGCG) on mesothelioma cells.[17]

Findings from one study reported in 2012 suggested that high-dose ascorbate increases radiosensitivity of glioblastoma multiforme cells, resulting in more cell death than from radiation therapy alone.[18]

However, not all studies combining vitamin C with chemotherapy have shown improved outcomes. Treating leukemia and lymphoma cells with dehydroascorbic acid (the oxidized form of vitamin C that increases levels of intracellular ascorbic acid) reduced the cytotoxic effects of various antineoplastic agents tested, including doxorubicin, methotrexate, and cisplatin (relative
reductions in cytotoxicity ranged from 30% to 70%).[19] In another study, multiple myeloma cells were treated with bortezomib and/or plasma obtained from healthy volunteers who had taken vitamin C supplements. Cells treated with a combination of bortezomib and volunteers’ plasma exhibited lower cytotoxicity than did cells treated with bortezomib alone.[20]

Animal Studies


The effects of high-dose ascorbic acid in combination with standard treatments on tumors have been investigated. In a mouse model of pancreatic cancer, the combination of gemcitabine (30 or 60 mg /kg every 4 days) and ascorbate (4 g /kg daily) resulted in greater decreases in tumor volume and weight, compared with gemcitabine treatment alone.[8] According to a study reported in 2012, ascorbate enhanced the cancer cell–killing effects of photodynamic therapy in mice injected with breast cancer cells.[23] A study of mouse models of ovarian cancer found that ascorbate enhanced the tumor inhibitory effect of carboplatin and paclitaxel, first-line chemotherapy used in ovarian cancer.[24]

Using N-acetylcysteine (NAC) and vitamin C, researchers showed in 2007 that these compounds, both thought to act predominantly as antioxidants, may have antitumorigenic actions in vivo by decreasing levels of hypoxia -inducible factor (HIF)-1, a transcription factor that targets vascular endothelial growth factor (VEGF) and plays a role in angiogenesis.[25]

There have also been reports of animal studies in which vitamin C has interfered with the anticancer activity of various drugs. In a study reported in 2008, administration of dehydroascorbic acid to lymphoma-xenograft mice prior to doxorubicin treatment resulted in significantly larger tumors than did treatment with doxorubicin alone.[19] Notably, this study used dehydroascorbate, the oxidized form of vitamin C that is known to be transported actively into cells and then reduced to vitamin C. Treating multiple myeloma xenograft mice with a combination of oral vitamin C and bortezomib resulted in significantly greater tumor volume than did treatment with bortezomib alone.[20] This increase in tumor volume was caused by a chemical reaction that occurs in the gastrointestinal tract but does not appear to be relevant to intravenous administration.

References


Human/Clinical Studies
Early Ascorbate-Only Trials

In the early 1970s, a consecutive case series was conducted in which 50 advanced-cancer patients were treated with large doses of ascorbic acid.[1] These patients began ascorbic acid treatment after conventional therapies were deemed unlikely to be effective. Patients received intravenous (IV) ascorbic acid (10 g /day for 10 consecutive days; some patients received higher doses), oral ascorbic acid (10 g/day), or both. The subjects exhibited a wide variety of responses to treatment, including no or minimal response, tumor regression, and tumor hemorrhage. However, the authors noted that lack of controls prevented definitive assignment of any beneficial responses to the ascorbic acid treatment. A case report published in 1975 detailed one of the patients who had experienced tumor regression.[2] Diagnosed with reticulum cell sarcoma, the patient exhibited improvement in well-being and resolution of lung masses after being treated with ascorbic acid. When the patient’s daily dose of ascorbic acid was reduced, some of signs of the disease returned; however, remission was achieved again after the patient reverted to the higher initial dose.

A larger case series of terminal cancer patients treated with ascorbate was reported in 1976. In this study, 100 terminal cancer patients (50 of whom were reported on previously) [1] were treated with ascorbate (10 g/day for 10 days IV, then orally) and compared with 1,000 matched controls from the same hospital. The mean survival time for ascorbate-treated patients was 300 days longer than that of the matched controls.[3,4]

Two studies tried to reproduce earlier results. These studies were randomized, placebo-controlled trials in which cancer patients received either 10 g oral vitamin C or placebo daily until signs of cancer progression. At the end of each study, no significant differences were noted between the two ascorbate-treated and placebo-treated groups for symptoms, performance status, or survival. [5,6]

Recent Ascorbate-Only Trials

One study reported three case reports of cancer patients who received IV vitamin C as their main therapy. During vitamin C therapy, the patients used additional treatments, including vitamins, minerals, and botanicals. According to the authors, the cases were reviewed in accordance with the NCI Best Case Series guidelines. Histopathologic examination suggested poor prognoses for these patients, but they had long survival times after being treated with IV vitamin C.[7] Vitamin C was given at doses ranging from 15 g to 65 g, initially once or twice a week for several months; two patients then received it less frequently for 1 to 4 years.

Two studies demonstrated that IV vitamin C treatment resulted in improved quality of life and decreases in cancer-related side effects in cancer patients.[8,9]
Studies have shown that vitamin C can be safely administered to healthy volunteers or cancer patients at doses up to 1.5 g/kg and with screening to eliminate treating individuals with risk factors for toxicity (e.g., glucose-6-phosphate dehydrogenase deficiency, renal diseases, or urolithiasis). These studies have also found that plasma concentrations of vitamin C are higher with IV administration than with oral administration and are maintained for more than 4 hours. [10,11]

**Ascorbate-Combination Trials**

A phase I study published in 2012 examined the safety and efficacy of combining IV ascorbate with gemcitabine and erlotinib in stage IV pancreatic cancer patients. Fourteen subjects entered the study and planned to receive IV gemcitabine (1,000 mg /m² over 30 minutes, once a week for 7 weeks), oral erlotinib (100 mg daily for 8 weeks), and IV ascorbate (50 g/infusion, 75 g/infusion, or 100 g/infusion 3 times per week for 8 weeks). Minimal adverse effects were reported for ascorbic acid treatment. Five subjects received fewer than 18 of the planned 24 ascorbate infusions and thus did not have follow-up imaging to assess response. Three of those patients had clinically determined progressive disease. All of the other nine patients had repeat imaging to assess tumor size, and each met the criteria for having stable disease.[12]

A 2013 phase I clinical study evaluated the safety of combining pharmacological ascorbate with gemcitabine in treating stage IV pancreatic cancer patients. During each 4-week cycle, patients received gemcitabine weekly for 3 weeks (1,000 mg/m² over 30 minutes) and twice weekly ascorbate infusions for 4 weeks (15 g over 30 minutes during the first week, followed by weekly escalations in dose until plasma levels reached at least 350 mg/dL [20 mM]). Among nine patients, mean progression-free survival was 26 weeks and overall survival was 12 months. The combination treatment was well tolerated, and no significant adverse events were reported.[13]

In 2014, a phase I/IIA clinical trial evaluated the toxicities of combining IV ascorbate with carboplatin and paclitaxel in stage III /IV ovarian cancer. Twenty-seven patients were randomly assigned to receive either chemotherapy alone or chemotherapy and IV vitamin C concurrently. Chemotherapy was given for 6 months, and IV vitamin C was given for 12 months. The addition of IV vitamin C was associated with reduced chemotherapy-related toxicities.[14]

Trials of high-dose IV vitamin C with other drugs are ongoing.[12,14] A number of studies have included IV ascorbic acid treatment (1,000 mg) with arsenic trioxide regimens, with mixed results. The combination therapies were well tolerated and suggested beneficial effects in multiple myeloma patients, although the specific contribution of vitamin C could not be determined.[15-18] However, similar combination regimens resulted in severe side effects and disease progression in patients with acute myeloid leukemia,[19] refractory metastatic colorectal cancer,[20] and
metastatic melanoma.[21]

Current Clinical Trials

Check NCI’s list of cancer clinical trials for cancer CAM clinical trials on ascorbic acid that are actively enrolling patients.

General information about clinical trials is also available from the NCI Web site.

References


9. Yeom CH, Jung GC, Song KJ: Changes of terminal cancer patients' health-related quality of life


Adverse Effects

Intravenous (IV) high-dose ascorbic acid has been generally well tolerated in clinical trials.[1-8] Renal failure following ascorbic acid treatment has been reported in patients with preexisting renal disorders.[9]

Case reports have indicated that patients with glucose-6-phosphate dehydrogenase (G-6-PD) deficiency should not receive high doses of vitamin C because of the risk of developing hemolysis.[10-12]

Vitamin C may increase bioavailability of iron, and high doses of the vitamin are not recommended for patients with hemochromatosis.[13]

Drug Interactions

When administered in high doses, vitamin C may result in adverse interactions with some anticancer agents. These interactions have primarily been detected in preclinical studies. A 2013 phase I clinical study evaluated the safety of combining high-dose IV ascorbate with gemcitabine in stage IV pancreatic cancer patients. The combination therapy was well tolerated by patients, and no significant adverse events were reported.[14]

*In vitro and in vivo* animal studies have suggested that combining oral vitamin C with bortezomib interferes with the drug’s ability to act as a proteasome inhibitor and blocks bortezomib-initiated apoptosis.[15-17] This interference occurred even with the oral administration of vitamin C (40 mg/kg/day) to animals. Studies in cell culture and performed by adding blood plasma from healthy volunteers given oral vitamin C (1 g/day) also showed a significant decrease in bortezomib’s growth inhibitory effect on multiple myeloma cells. Another study found similar results. Plasma from healthy volunteers who took 1 g of oral vitamin C per day was shown to decrease bortezomib growth inhibition in multiple myeloma cells and to block its inhibitory effect on 20S proteasome activity.[17] However, a study that utilized mice harboring human prostate cancer cell xenografts failed to find any significant effect of oral vitamin C (40 mg/kg/day or 500 mg/kg/day) on the tumor growth inhibitory action of bortezomib.[18]

Several studies have been performed to assess the potential synergistic or inhibitory action of vitamin C on certain chemotherapy drugs, with variable results. A series of studies in cell culture...
and in animals bearing tumors has shown that when given at high concentrations or dosages, dehydroascorbic acid (an oxidized form of vitamin C) can interfere with the cytotoxic effects of several chemotherapy drugs.\[19\] However, dehydroascorbic acid is generally present only at low concentrations in dietary supplements and fresh foods.

References


Changes to This Summary (06/29/2015)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

Editorial changes were made to this summary.

This summary is written and maintained by the PDQ Cancer Complementary and Alternative Medicine Editorial Board, which is editorially independent of NCI. The summary reflects an independent review of the literature and does not represent a policy statement of NCI or NIH. More information about summary policies and the role of the PDQ Editorial Boards in maintaining the PDQ summaries can be found on the About This PDQ Summary and PDQ NCI's
Comprehensive Cancer Database pages.

About This PDQ Summary

Purpose of This Summary

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the use of high-dose vitamin C in the treatment of people with cancer. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.

Reviewers and Updates

This summary is reviewed regularly and updated as necessary by the PDQ Cancer Complementary and Alternative Medicine Editorial Board, which is editorially independent of the National Cancer Institute (NCI). The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH).

Board members review recently published articles each month to determine whether an article should:

- be discussed at a meeting,
- be cited with text, or
- replace or update an existing article that is already cited.

Changes to the summaries are made through a consensus process in which Board members evaluate the strength of the evidence in the published articles and determine how the article should be included in the summary.

The lead reviewer for High-Dose Vitamin C is:

- Jeffrey D. White, MD (National Cancer Institute)

Any comments or questions about the summary content should be submitted to Cancer.gov through the Web site's Contact Form. Do not contact the individual Board Members with questions or comments about the summaries. Board members will not respond to individual inquiries.
Levels of Evidence

Some of the reference citations in this summary are accompanied by a level-of-evidence designation. These designations are intended to help readers assess the strength of the evidence supporting the use of specific interventions or approaches. The PDQ Cancer Complementary and Alternative Medicine Editorial Board uses a formal evidence ranking system in developing its level-of-evidence designations.

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Cannabis and Cannabinoids–for health professionals (PDQ®)

Overview

This complementary and alternative medicine (CAM) information summary provides an overview of the use of Cannabis and its components as a treatment for people with cancer-related symptoms caused by the disease itself or its treatment.

This summary contains the following key information:

- **Cannabis** has been used for medicinal purposes for thousands of years.
- By federal law, the possession of Cannabis, also known as marijuana, is illegal in the United States; however, a growing number of states and the District of Columbia have enacted laws to legalize its medical use.
- The U.S. Food and Drug Administration has not approved Cannabis as a treatment for cancer or any other medical condition.
- Chemical components of Cannabis, called cannabinoids, activate specific receptors found throughout the body to produce pharmacologic effects, particularly in the central nervous system and the immune system.
- Commercially available cannabinoids, such as dronabinol and nabilone, are approved drugs for the treatment of cancer-related side effects.
- Cannabinoids may have benefits in the treatment of cancer-related side effects.

Many of the medical and scientific terms used in this summary are hypertext linked (at first use in each section) to the NCI Dictionary of Cancer Terms, which is oriented toward nonexperts. When a linked term is clicked, a definition will appear in a separate window.

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or the National Cancer Institute.

**General Information**

*Cannabis*, also known as marijuana, originated in Central Asia but is grown worldwide today. In the United States, it is a controlled substance and is classified as a Schedule I agent (a drug with increased potential for abuse and no known medical use). The *Cannabis* plant produces a resin containing psychoactive compounds called cannabinoids. The highest concentration of cannabinoids is found in the female flowers of the plant.[1] Clinical trials conducted on medicinal *Cannabis* are limited. The U.S. Food and Drug Administration (FDA) has not approved the use of *Cannabis* as a treatment for any medical condition. To conduct clinical drug research in the United States, researchers must file an Investigational New Drug (IND) application with the FDA.

The potential benefits of medicinal *Cannabis* for people living with cancer include antiemetic effects, appetite stimulation, pain relief, and improved sleep. Although few relevant surveys of practice patterns exist, it appears that physicians caring for cancer patients in the United States who recommend medicinal *Cannabis* predominantly do so for symptom management.[2] A growing number of pediatric patients are seeking symptom relief with *Cannabis* or cannabinoid treatment, although studies are limited.

Cannabinoids are a group of terpenophenolic compounds found in *Cannabis* species (e.g., *Cannabis sativa* L.). This summary will review the role of *Cannabis* and the cannabinoids in the treatment of people with cancer and disease-related or treatment-related side effects.

**References**


**History**

*Cannabis* use for medicinal purposes dates back at least 3,000 years.[1-5] It was introduced into Western medicine in the 1840s by W.B. O’Shaughnessy, a surgeon who learned of its medicinal properties while working in India for the British East Indies Company. Its use was promoted for reported analgesic, sedative, anti-inflammatory, antispasmodic, and anticonvulsant effects.

In 1937, the U.S. Treasury Department introduced the Marihuana Tax Act. This Act imposed a levy
of $1 per ounce for medicinal use of Cannabis and $100 per ounce for recreational use. Physicians in the United States were the principal opponents of the Act. The American Medical Association (AMA) opposed the Act because physicians were required to pay a special tax for prescribing Cannabis, use special order forms to procure it, and keep special records concerning its professional use. In addition, the AMA believed that objective evidence that Cannabis was harmful was lacking and that passage of the Act would impede further research into its medicinal worth. [6] In 1942, Cannabis was removed from the U.S. Pharmacopoeia because of persistent concerns about its potential to cause harm.[2,3]

In 1951, Congress passed the Boggs Act, which for the first time, included Cannabis with narcotic drugs. In 1970, with the passage of the Controlled Substances Act, marijuana was classified as a Schedule I drug. Drugs in this category are distinguished as having no accepted medicinal use. Other Schedule I substances include heroin, LSD, mescaline, and methaqualone.

Despite its designation as having no medicinal use, Cannabis was distributed to patients by the U.S. government on a case-by-case basis under the Compassionate Use Investigational New Drug program established in 1978. Distribution of Cannabis through this program was discontinued in 1992.[1-4] Although federal law prohibits the use of Cannabis, the table below lists the localities that permit its use for certain medical conditions.

**List of Localities That Permit Use of Cannabis for Certain Medical Conditions**

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The main psychoactive constituent of Cannabis was identified as delta-9-tetrahydrocannabinol (THC). In 1986, synthetic delta-9-THC in sesame oil was licensed and approved for the treatment of chemotherapy-associated nausea and vomiting under the generic name dronabinol. Clinical trials determined that dronabinol was as effective as or better than other antiemetic agents available at the time.[7] Dronabinol was also studied for its ability to stimulate weight gain in patients with AIDS in the late 1980s. Thus, the indications were expanded to include treatment of anorexia associated with human immunodeficiency virus infection in 1992. Clinical trial results showed no statistically significant weight gain, although patients reported an improvement in appetite.[8,9]

Within the past 20 years, the neurobiology of cannabinoids has been analyzed.[10-13] The first cannabinoid receptor, CB1, was identified in the brain in 1988. A second cannabinoid receptor, CB2, was identified in 1993. The highest expression of CB2 receptors is located on B lymphocytes and natural killer cells, suggesting a possible role in immunity. Endogenous cannabinoids (endocannabinoids) have been identified and appear to have a role in, for example, pain modulation, control of movement, feeding behavior, and memory.[11]

Spasticity is a common symptom of multiple sclerosis for which existing therapy is unsatisfactory and may include muscle stiffness, reduced mobility, and pain. In Canada, New Zealand, and some countries in Europe, nabiximols (a THC:cannabidiol extract) is approved for the treatment of spasticity associated with multiple sclerosis via oromucosal administration.[14,15] Nabiximols is also approved in Canada (under the Notice of Compliance with Conditions) for symptomatic relief of pain in multiple sclerosis and advanced cancer.[15]

References


Laboratory/Animal/Preclinical Studies

Cannabinoids are a group of 21-carbon–containing terpenophenolic compounds produced uniquely by Cannabis species (e.g., Cannabis sativa L.).[1,2] These plant-derived compounds may be referred to as phytocannabinoids. Although delta-9-tetrahydrocannabinol (THC) is the primary psychoactive ingredient, other known compounds with biologic activity are cannabinol, cannabidiol (CBD), cannabichromene, cannabigerol, tetrahydrocannabivarin, and delta-8-THC. CBD, in particular, is thought to have significant analgesic and anti-inflammatory activity without the psychoactive effect (high) of delta-9-THC.

Antitumor Effects

One study in mice and rats suggested that cannabinoids may have a protective effect against the development of certain types of tumors.[3] During this 2-year study, groups of mice and rats were given various doses of THC by gavage. A dose-related decrease in the incidence of hepatic adenoma tumors and hepatocellular carcinoma (HCC) was observed in the mice. Decreased incidences of benign tumors (polyps and adenomas) in other organs (mammary gland, uterus, pituitary, testis, and pancreas) were also noted in the rats. In another study, delta-9-THC, delta-8-THC, and cannabinol were found to inhibit the growth of Lewis lung adenocarcinoma cells in vitro and in vivo.[4] In addition, other tumors have been shown to be sensitive to cannabinoid-induced growth inhibition.[5-8]

Cannabinoids may cause antitumor effects by various mechanisms, including induction of cell death, inhibition of cell growth, and inhibition of tumor angiogenesis invasion and metastasis.[9-12] Two reviews summarize the molecular mechanisms of action of cannabinoids as antitumor agents.[13,14] Cannabinoids appear to kill tumor cells but do not affect their nontransformed counterparts and may even protect them from cell death. For example, these compounds have been shown to induce apoptosis in glioma cells in culture and induce regression of glioma tumors in mice and rats, while they protect normal glial cells of astroglial and oligodendroglial lineages from apoptosis mediated by the CB1 receptor.[9]

The effects of delta-9-THC and a synthetic agonist of the CB2 receptor were investigated in HCC.[15] Both agents reduced the viability of HCC cells in vitro and demonstrated antitumor effects in HCC subcutaneous xenografts in nude mice. The investigations documented that the anti-HCC effects are mediated by way of the CB2 receptor. Similar to findings in glioma cells, the cannabinoids were shown to trigger cell death through stimulation of an endoplasmic reticulum stress pathway that activates autophagy and promotes apoptosis. Other investigations have confirmed that CB1 and CB2 receptors may be potential targets in non-small cell lung carcinoma[16] and breast cancer.[17]
An *in vitro* study of the effect of CBD on programmed cell death in breast cancer cell lines found that CBD induced programmed cell death, independent of the CB1, CB2, or vanilloid receptors. CBD inhibited the survival of both estrogen receptor–positive and estrogen receptor–negative breast cancer cell lines, inducing apoptosis in a concentration-dependent manner while having little effect on nontumorigenic mammary cells.[18] Other studies have also shown the antitumor effect of cannabinoids (i.e., CBD and THC) in preclinical models of breast cancer.[19,20]

CBD has also been demonstrated to exert a chemopreventive effect in a mouse model of colon cancer.[21] In this experimental system, azoxymethane increased premalignant and malignant lesions in the mouse colon. Animals treated with azoxymethane and CBD concurrently were protected from developing premalignant and malignant lesions. In *in vitro* experiments involving colorectal cancer cell lines, the investigators found that CBD protected DNA from oxidative damage, increased endocannabinoid levels, and reduced cell proliferation. In a subsequent study, the investigators found that the antiproliferative effect of CBD was counteracted by selective CB1 but not CB2 receptor antagonists, suggesting an involvement of CB1 receptors.[22]

Another investigation into the antitumor effects of CBD examined the role of intercellular adhesion molecule-1 (ICAM-1).[12] ICAM-1 expression has been reported to be negatively correlated with cancer metastasis. In lung cancer cell lines, CBD upregulated ICAM-1, leading to decreased cancer cell invasiveness.

In an *in vivo* model using severe combined immunodeficient mice, subcutaneous tumors were generated by inoculating the animals with cells from human non-small cell lung carcinoma cell lines.[23] Tumor growth was inhibited by 60% in THC-treated mice compared with vehicle-treated control mice. Tumor specimens revealed that THC had antiangiogenic and antiproliferative effects. However, research with immunocompetent murine tumor models has demonstrated immunosuppression and enhanced tumor growth in mice treated with THC.[24,25]

In addition, both plant-derived and endogenous cannabinoids have been studied for anti-inflammatory effects. A mouse study demonstrated that endogenous cannabinoid system signaling is likely to provide intrinsic protection against colonic inflammation.[26] As a result, a hypothesis that phytocannabinoids and endocannabinoids may be useful in the risk reduction and treatment of colorectal cancer has been developed.[27-30]

CBD may also enhance uptake of cytotoxic drugs into malignant cells. Activation of the transient receptor potential vanilloid type 2 (TRPV2) has been shown to inhibit proliferation of human glioblastoma multiforme cells and overcome resistance to the chemotherapy agent carmustine. [31] In an *in vitro* model, CBD increased TRPV2 activation and increased uptake of cytotoxic drugs, leading to apoptosis of glioma cells without affecting normal human astrocytes. This suggests that coadministration of CBD with cytotoxic agents may increase drug uptake and potentiate cell
death in human glioma cells. Also, CBD together with THC may enhance the antitumor activity of classic chemotherapeutic drugs such as temozolomide in some mouse models of cancer.[13,32]

**Appetite Stimulation**

Many animal studies have previously demonstrated that delta-9-THC and other cannabinoids have a stimulatory effect on appetite and increase food intake. It is believed that the endogenous cannabinoid system may serve as a regulator of feeding behavior. The endogenous cannabinoid anandamide potently enhances appetite in mice.[33] Moreover, CB1 receptors in the hypothalamus may be involved in the motivational or reward aspects of eating.[34]

**Analgesia**

Understanding the mechanism of cannabinoid-induced analgesia has been increased through the study of cannabinoid receptors, endocannabinoids, and synthetic agonists and antagonists. The CB1 receptor is found in both the central nervous system (CNS) and in peripheral nerve terminals. Similar to opioid receptors, increased levels of the CB1 receptor are found in regions of the brain that regulate nociceptive processing.[35] CB2 receptors, located predominantly in peripheral tissue, exist at very low levels in the CNS. With the development of receptor-specific antagonists, additional information about the roles of the receptors and endogenous cannabinoids in the modulation of pain has been obtained.[36,37]

Cannabinoids may also contribute to pain modulation through an anti-inflammatory mechanism; a CB2 effect with cannabinoids acting on mast cell receptors to attenuate the release of inflammatory agents, such as histamine and serotonin, and on keratinocytes to enhance the release of analgesic opioids has been described.[38-40] One study reported that the efficacy of synthetic CB1- and CB2-receptor agonists were comparable with the efficacy of morphine in a murine model of tumor pain.[41]

**References**

3. National Toxicology Program: NTP toxicology and carcinogenesis studies of 1-trans-delta(9)-tetrahydrocannabinol (CAS No. 1972-08-3) in F344 rats and B6C3F1 mice (gavage studies). Natl Toxicol Program Tech Rep Ser 446 (): 1-317, 1996. [PUBMED Abstract]


Human/Clinical Studies

**Cannabis Pharmacology**

When *Cannabis* is ingested by mouth, there is a low (6%–20%) and variable oral bioavailability.[1,2] Peak plasma concentrations of delta-9-tetrahydrocannabinol (THC) occur after 1 to 6 hours and remain elevated with a terminal half-life of 20 to 30 hours. Taken by mouth, delta-9-THC is initially metabolized in the liver to 11-OH-THC, a potent psychoactive metabolite. When inhaled, cannabinoids are rapidly absorbed into the bloodstream with a peak concentration in 2 to 10 minutes, declining rapidly for a period of 30 minutes and with less generation of the psychoactive 11-OH metabolite.

Cannabinoids are known to interact with the hepatic cytochrome P450 enzyme system.[3,4] In one study, 24 cancer patients were treated with intravenous irinotecan (600 mg, n = 12) or docetaxel (180 mg, n = 12), followed 3 weeks later by the same drugs concomitant with medicinal *Cannabis* taken in the form of an herbal tea for 15 consecutive days, starting 12 days before the second treatment.[4] The administration of *Cannabis* did not significantly influence exposure to and clearance of irinotecan or docetaxel, although the herbal tea route of administration may not reproduce the effects of inhalation or oral ingestion of fat-soluble cannabinoids.

**Cancer Risk**

A number of studies have yielded conflicting evidence regarding the risks of various cancers associated with *Cannabis* use.

A pooled analysis of three case-cohort studies of men in northwestern Africa (430 cases and 778 controls) showed a significantly increased risk of lung cancer among tobacco smokers who also inhaled *Cannabis*.[5]

A large, retrospective cohort study of 64,855 men aged 15 to 49 years from the United States found that *Cannabis* use was not associated with tobacco-related cancers and a number of other common malignancies. However, the study did find that, among nonsmokers of tobacco, ever having used *Cannabis* was associated with an increased risk of prostate cancer.[6]

A population-based case-control study of 611 lung cancer patients revealed that chronic low *Cannabis* exposure was not associated with an increased risk of lung cancer or other upper aerodigestive tract cancers and found no positive associations with any cancer type (oral, pharyngeal, laryngeal, lung, or esophagus) when adjusting for several confounders, including cigarette smoking.[7]
A systematic review assessing 19 studies that evaluated premalignant or malignant lung lesions in persons 18 years or older who inhaled marijuana concluded that observational studies failed to demonstrate statistically significant associations between marijuana inhalation and lung cancer after adjusting for tobacco use.[8]

Epidemiologic studies examining one association of Cannabis use with head and neck squamous cell carcinomas have also been inconsistent in their findings. A pooled analysis of nine case-control studies from the U.S./Latin American International Head and Neck Cancer Epidemiology (INHANCE) Consortium included information from 1,921 oropharyngeal cases, 356 tongue cases, and 7,639 controls. Compared with those who never smoked Cannabis, Cannabis smokers had an elevated risk of oropharyngeal cancers and a reduced risk of tongue cancer. These study results both reflect the inconsistent effects of cannabinoids on cancer incidence noted in previous studies and suggest that more work needs to be done to understand the potential role of human papillomavirus infection.[9]

With a hypothesis that chronic marijuana use produces adverse effects on the human endocrine and reproductive systems, the association between marijuana use and incidence of testicular germ cell tumors (TGCTs) has been examined.[10-12] Three population-based case-control studies report an association between marijuana use and elevated risk of TGCTs, especially nonseminoma or mixed-histology tumors.[10-12] However, the sample sizes in these studies were inadequate to address marijuana dose by addressing associations with respect to recency, frequency, and duration of use. These early reports of marijuana use and TGCTs establish the need for larger, well-powered, prospective studies, especially studies evaluating the role of endocannabinoid signaling and cannabinoid receptors in TGCTs.

An analysis of 84,170 participants in the California Men’s Health Study was performed to investigate the association between Cannabis use and the incidence of bladder cancer. During 16 years of follow-up, 89 Cannabis users (0.3%) developed bladder cancer compared with 190 (0.4%) of the men who did not report Cannabis use (P < .001). After adjusting for age, race, ethnicity, and body mass index, Cannabis use was associated with a 45% reduction in bladder cancer incidence (hazard ratio, 0.55; 95% confidence interval, 0.33–1.00).[13]

A comprehensive Health Canada monograph on marijuana concluded that while there are many cellular and molecular studies that provide strong evidence that inhaled marijuana is carcinogenic, the epidemiologic evidence of a link between marijuana use and cancer is still inconclusive.[14]

Cancer Treatment

No clinical trials of Cannabis as a treatment for cancer in humans were identified in a PubMed
search; however, a single, small study of intratumoral injection of delta-9-THC in patients with recurrent glioblastoma multiforme reported potential antitumoral activity.[15,16]

**Antiemetic Effect**

**Cannabinoids**

Despite advances in pharmacologic and nonpharmacologic management, nausea and vomiting (N/V) remain distressing side effects for cancer patients and their families. Dronabinol, a synthetically produced delta-9-THC, was approved in the United States in 1986 as an antiemetic to be used in cancer chemotherapy. Nabilone, a synthetic derivative of delta-9-THC, was first approved in Canada in 1982 and is now also available in the United States.[17] Both dronabinol and nabilone have been approved by the U.S. Food and Drug Administration for the treatment of N/V associated with cancer chemotherapy in patients who have failed to respond to conventional antiemetic therapy. Numerous clinical trials and meta-analyses have shown that dronabinol and nabilone are effective in the treatment of N/V induced by chemotherapy.[18-21] The National Comprehensive Cancer Network Guidelines recommend cannabinoids as breakthrough treatment for chemotherapy-related N/V.

One systematic review studied 30 randomized comparisons of delta-9-THC preparations with placebo or other antiemetics from which data on efficacy and harm were available.[22] Oral nabilone, oral dronabinol, and intramuscular levonantradol (a synthetic analog of dronabinol) were tested. Inhaled Cannabis trials were not included. Among all 1,366 patients included in the review, cannabinoids were found to be more effective than the conventional antiemetics prochlorperazine, metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone, and alizapride. Cannabinoids, however, were not more effective for patients receiving very low or very high emetogenic chemotherapy. Side effects included a feeling of being high, euphoria, sedation or drowsiness, dizziness, dysphoria or depression, hallucinations, paranoia, and hypotension.[22] Newer antiemetics (e.g., 5-HT3 receptor antagonists) have not been directly compared with Cannabis or cannabinoids in cancer patients.

Another analysis of 15 controlled studies compared nabilone with placebo or available antiemetic drugs.[23] Among 600 cancer patients, nabilone was found to be superior to prochlorperazine, domperidone, and alizapride, with nabilone favored for continuous use.

(Refer to the Cannabis section in the PDQ summary on Nausea and Vomiting for more information.)

**Cannabis**
Three trials have evaluated the efficacy of inhaled marijuana in chemotherapy-induced N/V.[24-26] In two of the studies, inhaled Cannabis was made available only after dronabinol failure. In the first trial, no antiemetic effect was achieved with marijuana in patients receiving cyclophosphamide or doxorubicin,[24] but in the second trial, a statistically significant superior antiemetic effect of inhaled Cannabis versus placebo was found among patients receiving high-dose methotrexate.[25] The third trial was a randomized, double-blind, placebo-controlled, cross-over trial involving 20 adults in which both inhaled marijuana and oral THC were evaluated. One-quarter of the patients reported a favorable antiemetic response to the cannabinoid therapies. This latter study was reported in abstract form in 1984. A full report, detailing the methods and outcomes apparently has not been published, which limits a thorough interpretation of the significance of these findings.[26]

**Appetite Stimulation**

Anorexia, early satiety, weight loss, and cachexia are problems experienced by cancer patients. Such patients are faced not only with the disfigurement associated with wasting but also with an inability to engage in the social interaction of meals.

**Cannabinoids**

Three controlled trials demonstrated that oral THC has variable effects on appetite stimulation and weight loss in patients with advanced malignancies and human immunodeficiency virus (HIV) infection.[23] One study evaluated whether dronabinol alone or with megestrol acetate was greater, less, or equal in efficacy to megestrol acetate alone for managing cancer-associated anorexia.[27] In this randomized, double-blind study of 469 adults with advanced cancer and weight loss, patients received 2.5 mg of oral THC twice daily, 800 mg of oral megestrol daily, or both. Appetite increased by 75% in the megestrol group and weight increased by 11%, compared with a 49% increase in appetite and a 3% increase in weight in the oral THC group after 8 to 11 weeks of treatment. These two differences were statistically significant. Furthermore, the combined therapy did not offer additional benefits beyond those provided by megestrol acetate alone. The authors concluded that dronabinol did little to promote appetite or weight gain in advanced cancer patients compared with megestrol acetate. However, a smaller, placebo-controlled trial of dronabinol in cancer patients demonstrated improved and enhanced chemosensory perception in the cannabinoid group—food tasted better, appetite increased, and the proportion of calories consumed as protein was greater than in the placebo recipients.[28]

In a randomized clinical trial, researchers compared the safety and effectiveness of orally administered Cannabis extract (2.5 mg THC and 1 mg cannabidiol), THC (2.5 mg), or placebo for the treatment of cancer-related anorexia-cachexia in 243 patients with advanced cancer who
received treatment twice daily for 6 weeks. Results demonstrated that although these agents were well tolerated by these patients, no differences were observed in patient appetite or quality of life among the three groups at this dose level and duration of intervention.[29]

Another clinical trial that involved 139 patients with HIV or AIDS and weight loss found that, compared with placebo, oral dronabinol was associated with a statistically significant increase in appetite after 4 to 6 weeks of treatment. Patients receiving dronabinol tended to have weight stabilization, whereas patients receiving placebo continued to lose weight.[30]

**Cannabis**

In trials conducted in the 1980s that involved healthy control subjects, inhaling Cannabis led to an increase in caloric intake, mainly in the form of between-meal snacks, with increased intakes of fatty and sweet foods.[31,32] No published studies have explored the effect of inhaled Cannabis on appetite in cancer patients.

**Analgesia**

**Cannabinoids**

Pain management improves a patient’s quality of life throughout all stages of cancer. Through the study of cannabinoid receptors, endocannabinoids, and synthetic agonists and antagonists, the mechanisms of cannabinoid-induced analgesia have been analyzed. The CB1 receptor is found in the central nervous system (CNS) and in peripheral nerve terminals.[33] CB2 receptors are located mainly in peripheral tissue and are expressed in only low amounts in the CNS. Whereas only CB1 agonists exert analgesic activity in the CNS, both CB1 and CB2 agonists have analgesic activity in peripheral tissue.[34,35]

Cancer pain results from inflammation, invasion of bone or other pain-sensitive structures, or nerve injury. When cancer pain is severe and persistent, it is often resistant to treatment with opioids.

Two studies examined the effects of oral delta-9-THC on cancer pain. The first, a double-blind placebo-controlled study involving ten patients, measured both pain intensity and pain relief.[36] It was reported that 15 mg and 20 mg doses of the cannabinoid delta-9-THC were associated with substantial analgesic effects, with antiemetic effects and appetite stimulation.

In a follow-up, single-dose study involving 36 patients, it was reported that 10 mg doses of delta-9-THC produced analgesic effects during a 7-hour observation period that were comparable to 60 mg doses of codeine, and 20 mg doses of delta-9-THC induced effects equivalent to 120 mg doses of codeine.[37] Higher doses of THC were found to be more sedative than codeine.
Another study examined the effects of a whole-plant extract with controlled cannabinoid content in an oromucosal spray. In a multicenter, double-blind, placebo-controlled study, the THC:cannabidiol nabiximols (THC:CBD) extract and THC extract alone were compared in the analgesic management of patients with advanced cancer and with moderate-to-severe cancer-related pain. Patients were assigned to one of three treatment groups: THC:CBD extract, THC extract, or placebo. The researchers concluded that the THC:CBD extract was efficacious for pain relief in advanced cancer patients whose pain was not fully relieved by strong opioids.[38] In a randomized, placebo-controlled, graded-dose trial, opioid-treated cancer patients with poorly controlled chronic pain demonstrated significantly better control of pain and sleep disruption with THC:CBD oromucosal spray at lower doses (1–4 and 6–10 sprays/day), compared with placebo. Adverse events were dose related, with only the high-dose group (11–16 sprays/day) comparing unfavorably with the placebo arm. These studies provide promising evidence of an “adjuvant analgesic” effect of THC:CBD in this opioid-refractory patient population and may provide an opportunity to address this significant clinical challenge.[39] An open-label extension study of 43 patients who had participated in the randomized trial found that some patients continued to obtain relief of their cancer-related pain with long-term use of the THC:CBD oromucosal spray without increasing their dose of the spray or the dose of their other analgesics.[40]

A randomized, placebo-controlled, crossover pilot study of nabiximols in 16 patients with chemotherapy-induced neuropathic pain showed no significant difference between the treatment and placebo groups. A responder analysis, however, demonstrated that five patients reported a reduction in their pain of at least 2 points, suggesting that a larger follow-up study may be warranted.[41]

An observational study assessed the effectiveness of nabilone in advanced cancer patients who were experiencing pain and other symptoms (anorexia, depression, and anxiety). The researchers reported that patients who used nabilone experienced improved management of pain, nausea, anxiety, and distress when compared with untreated patients. Nabilone was also associated with a decreased use of opioids, nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, gabapentin, dexamethasone, metoclopramide, and ondansetron.[42]

**Cannabis**

Animal studies have suggested a synergistic analgesic effect when cannabinoids are combined with opioids. The results from one pharmacokinetic interaction study have been reported. In this study, 21 patients with chronic pain were administered vaporized Cannabis along with sustained-release morphine or oxycodone for 5 days.[43] The patients who received vaporized Cannabis and sustained-release morphine had a statistically significant decrease in their mean pain score over
the 5-day period; those who received vaporized Cannabis and oxycodone did not. These findings should be verified by further studies before recommendations favoring such an approach are warranted in general clinical practice.

Neuropathic pain is a symptom cancer patients may experience, especially if treated with platinum-based chemotherapy or taxanes. To date, no clinical trial has examined the effectiveness of cannabinoid preparations in the treatment of chemotherapy-induced neuropathic pain. Two randomized controlled trials of inhaled Cannabis in patients with peripheral neuropathy or neuropathic pain of various etiologies found that pain was reduced in patients who received inhaled Cannabis, compared with those who received placebo.[44,45] Two additional trials of inhaled Cannabis have also demonstrated the benefit of Cannabis over placebo in HIV-associated neuropathic pain.[46,47]

Anxiety and Sleep

Cannabis

Patients often experience mood elevation after exposure to Cannabis, depending on their prior experience. In a five-patient case series of inhaled marijuana that examined the analgesic effects of THC, it was reported that patients administered THC had improved mood, improved sense of well-being, and less anxiety.[48]

Another common effect of Cannabis is sleepiness. In a trial of a sublingual spray, a Cannabis-based mixture was able to improve sleep quality.[49] A small placebo-controlled study of dronabinol in cancer patients with altered chemosensory perception also noted increased quality of sleep and relaxation in THC-treated patients.[28]

Current Clinical Trials

Check NCI’s list of cancer clinical trials for cancer CAM clinical trials on dronabinol, marijuana, nabiximols, nabilone and cannabidiol that are actively enrolling patients.

General information about clinical trials is also available from the NCI Web site.

References


21-43, 1986. [PUBMED Abstract]


**Adverse Effects**

*Cannabis* and Cannabinoids
Because cannabinoid receptors, unlike opioid receptors, are not located in the brainstem areas controlling respiration, lethal overdoses from Cannabis and cannabinoids do not occur.[1-4] However, cannabinoid receptors are present in other tissues throughout the body, not just in the central nervous system, and adverse effects include tachycardia, hypotension, conjunctival injection, bronchodilation, muscle relaxation, and decreased gastrointestinal motility.

Although cannabinoids are considered by some to be addictive drugs, their addictive potential is considerably lower than that of other prescribed agents or substances of abuse.[2,4] The brain develops a tolerance to cannabinoids.

Withdrawal symptoms such as irritability, insomnia with sleep electroencephalogram disturbance, restlessness, hot flashes, and, rarely, nausea and cramping have been observed. However, these symptoms appear to be mild compared with withdrawal symptoms associated with opiates or benzodiazepines, and the symptoms usually dissipate after a few days.

Unlike other commonly used drugs, cannabinoids are stored in adipose tissue and excreted at a low rate (half-life 1–3 days), so even abrupt cessation of cannabinoid intake is not associated with rapid declines in plasma concentrations that would precipitate severe or abrupt withdrawal symptoms or drug cravings.

Since Cannabis smoke contains many of the same components as tobacco smoke, there are valid concerns about the adverse pulmonary effects of inhaled Cannabis. A longitudinal study in a noncancer population evaluated repeated measurements of pulmonary function over 20 years in 5,115 men and women whose smoking histories were known.[5] While tobacco exposure was associated with decreased pulmonary function, the investigators concluded that occasional and low-cumulative Cannabis use was not associated with adverse effects on pulmonary function (forced expiratory volume in the first second of expiration [FEV1] and forced vital capacity [FVC]).

References


**Summary of the Evidence for Cannabis and Cannabinoids**

To assist readers in evaluating the results of human studies of complementary and alternative medicine (CAM) treatments for people with cancer, the strength of the evidence (i.e., the levels of evidence) associated with each type of treatment is provided whenever possible. To qualify for a level of evidence analysis, a study must:

- Be published in a peer-reviewed scientific journal.
- Report on therapeutic outcome or outcomes, such as tumor response, improvement in survival, or measured improvement in quality of life.
- Describe clinical findings in sufficient detail for a meaningful evaluation to be made.

Separate levels of evidence scores are assigned to qualifying human studies on the basis of statistical strength of the study design and scientific strength of the treatment outcomes (i.e., endpoints) measured. The resulting two scores are then combined to produce an overall score. An overall level of evidence score cannot be assigned to cannabinoids because there has been insufficient clinical research to date. For an explanation of possible scores and additional information about levels of evidence analysis of CAM treatments for people with cancer, refer to **Levels of Evidence for Human Studies of Cancer Complementary and Alternative Medicine**.

**Cannabinoids**

Several controlled clinical trials have been performed, and meta-analyses of these support a beneficial effect of cannabinoids (dronabinol and nabilone) on chemotherapy-induced nausea and vomiting (N/V) compared with placebo. Both dronabinol and nabilone are approved by the U.S. Food and Drug Administration for the prevention or treatment of chemotherapy-induced N/V in cancer patients but not for other symptom management or off-label use.

**Cannabis**

- There have been only three small clinical trials on the use of *Cannabis* in cancer patients. All three studies assessed antiemetic activity but each explored a different patient population and chemotherapy regimen. One study demonstrated no effect, the second study showed a positive effect versus placebo, and the report of the third study did not provide enough
information to characterize the overall outcome as positive or neutral. Consequently, there are insufficient data to provide an overall level of evidence assessment for the use of Cannabis for chemotherapy-induced N/V. Apparently, there are no published data on the use of Cannabis for other cancer-related or cancer treatment–related symptoms.

• An increasing number of trials are evaluating the oromucosal administration of whole Cannabis plant extract with fixed concentrations of cannabinoid components.

• At present, there is insufficient evidence to recommend inhaling Cannabis as a treatment for cancer-related symptoms or cancer treatment–related side effects.

Changes to This Summary (07/16/2015)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

Human/Clinical Studies

Added text about an analysis of 84,170 participants in the California Men's Health Study that investigated the association between Cannabis use and the incidence of bladder cancer; after adjusting for age, race, ethnicity, and body mass index, Cannabis use was associated with a 45% reduction in bladder cancer incidence (cited Thomas et al. as reference 13).

This summary is written and maintained by the PDQ Cancer Complementary and Alternative Medicine Editorial Board, which is editorially independent of NCI. The summary reflects an independent review of the literature and does not represent a policy statement of NCI or NIH. More information about summary policies and the role of the PDQ Editorial Boards in maintaining the PDQ summaries can be found on the About This PDQ Summary and PDQ NCI's Comprehensive Cancer Database pages.

About This PDQ Summary

Purpose of This Summary

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the use of Cannabis and cannabinoids in the treatment of people with cancer. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.
Reviewers and Updates

This summary is reviewed regularly and updated as necessary by the PDQ Cancer Complementary and Alternative Medicine Editorial Board, which is editorially independent of the National Cancer Institute (NCI). The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH).

Board members review recently published articles each month to determine whether an article should:

- be discussed at a meeting,
- be cited with text, or
- replace or update an existing article that is already cited.

Changes to the summaries are made through a consensus process in which Board members evaluate the strength of the evidence in the published articles and determine how the article should be included in the summary.

The lead reviewers for Cannabis and Cannabinoids are:

- Donald I. Abrams, MD (UCSF Osher Center for Integrative Medicine)
- Nagi B. Kumar, PhD, RD, FADA (Fellow of the American Dietetic Association)

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Levels of Evidence

Some of the reference citations in this summary are accompanied by a level-of-evidence designation. These designations are intended to help readers assess the strength of the evidence supporting the use of specific interventions or approaches. The PDQ Cancer Complementary and Alternative Medicine Editorial Board uses a formal evidence ranking system in developing its level-of-evidence designations.

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Updated: July 16, 2015

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Overview

NOTE: The information in this summary is no longer being updated and is provided for reference purposes only.

This complementary and alternative medicine (CAM) information summary provides an overview of the use of cartilage as a treatment for people with cancer. The summary includes a brief history of cartilage research, the results of clinical studies, and possible side effects of cartilage use.

This summary contains the following key information:

- Bovine (cow) cartilage and shark cartilage have been studied as treatments for people with cancer and other medical conditions for more than 30 years.

- Numerous cartilage products are sold commercially in the United States as dietary supplements.

- Three principal mechanisms of action have been proposed to explain the antitumor potential of cartilage: (1) it kills cancer cells directly; (2) it stimulates the immune system; and (3) it blocks the formation of new blood vessels (angiogenesis), which tumors need for unrestricted growth.

- At least three different inhibitors of angiogenesis have been identified in bovine cartilage, and two angiogenesis inhibitors have been purified from shark cartilage.

- Few human studies of cartilage as a treatment for people with cancer have been reported to date, and the results are inconclusive.

- Additional clinical trials of cartilage as a treatment for people with cancer are now being conducted.

Many of the medical and scientific terms used in this summary are hypertext linked (at first use in each section) to the NCI Dictionary of Cancer Terms, which is oriented toward nonexperts. When a linked term is clicked, a definition will appear in a separate window.
Reference citations in some PDQ CAM information summaries may include links to external Web sites that are operated by individuals or organizations for the purpose of marketing or advocating the use of specific treatments or products. These reference citations are included for informational purposes only. Their inclusion should not be viewed as an endorsement of the content of the Web sites, or of any treatment or product, by the PDQ Cancer CAM Editorial Board or the National Cancer Institute.

General Information

Bovine (cow) cartilage and shark cartilage have been investigated as treatments for people with cancer, psoriasis, arthritis, and a number of other medical conditions for more than 30 years.[1-19] At least some of the interest in cartilage as a treatment for people with cancer arose from the mistaken belief that sharks, whose skeletons are made primarily of cartilage, are not affected by this disease.[16,20,21] Although reports of malignant tumors in sharks are rare, a variety of cancers have been detected in these animals.[20-23] Nonetheless, several substances that have antitumor activity have been identified in cartilage.[2-4,7,15-19,24-49] More than half a dozen clinical studies of cartilage as a treatment for people with cancer have already been conducted.[2-4,6-9,15-18,49,50] Additional clinical studies, MDA-ID-99303 and AETERNA-AE-MM-00-02 have been completed.[6,15,50]

The absence of blood vessels in cartilage led to the hypothesis that cartilage cells (also known as chondrocytes) produce one or more substances that inhibit blood vessel formation.[27-30,35,36,48] The formation of new blood vessels or angiogenesis is necessary for tumors to grow larger than a few millimeters in diameter (i.e., larger than approximately 100,000 to 1,000,000 cells) because tumors, like normal tissues, must obtain most of their oxygen and nutrients from blood.[33,34,41,51-54] A developing tumor, therefore, cannot continue to grow unless it establishes connections to the circulatory system of its host. It has been reported that tumors can initiate the process of angiogenesis when they contain as few as 100 cells.[53] Inhibition of angiogenesis at this early stage may, in some instances, lead to complete tumor regression.[53]

The possibility that cartilage could be a source of one or more types of angiogenesis inhibitors for the treatment of cancer has prompted much research.

The major structural components of cartilage include several types of the protein collagen and several types of glycosaminoglycans, which are polysaccharides.[19,29,30,39,48,54,55] Chondroitin sulfate is the major glycosaminoglycan in cartilage.[39,54] Although there is no evidence that the collagens in cartilage, or their breakdown products, can inhibit angiogenesis, there is evidence that shark cartilage contains at least one angiogenesis inhibitor that has a glycosaminoglycan component (refer to the Laboratory/Animal/Preclinical Studies section of this summary for more
Other data indicate that most of the antiangiogenic activity in cartilage is not associated with the major structural components.[26,30,48] Some glycosaminoglycans in cartilage reportedly have anti-inflammatory and immune-system-stimulating properties,[1,2,14,16,56,57] and it has been suggested that either they or some of their breakdown products are toxic to tumor cells.[2,3,24] Thus, the antitumor potential of cartilage may involve more than one mechanism of action.

Cartilage products are sold commercially in the United States as dietary supplements. More than 40 different brand names of shark cartilage alone are available to consumers.[17] In the United States, dietary supplements are regulated as foods, not drugs. Therefore, premarket evaluation and approval by the U.S. Food and Drug Administration (FDA) are not required unless specific disease prevention or treatment claims are made. Because manufacturers of cartilage products are not required to show evidence of anticancer or other biologic effects, it is unclear whether any of these products have therapeutic potential. In addition, individual products may vary considerably from lot to lot because standard manufacturing processes do not exist, and binding agents and fillers may be added during production.[17] The FDA has not approved the use of cartilage as a treatment for people with cancer or any other medical condition. The FDA is notifying consumers of a refund program for purchasers of Lane Labs-USA, Inc.'s shark cartilage product, BeneFin. Consumers are eligible for a partial refund of the purchase price and any shipping and handling costs if this product was purchased between September 22, 1999 and July 12, 2004.

To conduct clinical drug research in the United States, researchers must file an Investigational New Drug (IND) application with the FDA. To date, IND status has been granted to at least four groups of investigators, one of which was the MDA-ID-99303 trial, that is now closed, to study cartilage as a treatment for people with cancer.[7,18,58] Because the IND application process is confidential and because the existence of an IND can be disclosed only by the applicants, it is not known whether other applications have been made.

In animal studies, cartilage products have been administered in a variety of ways. In some studies, oral administration of either liquid or powdered forms has been used.[19,39,40,43,44,59,15,47] In other studies, cartilage products have been given by injection (intravenous or intraperitoneal), applied topically, or placed in slow-release plastic pellets that were surgically implanted.[26-28,32,33,35,38,40,42,44,46,48] Most of the latter studies investigated the effects of cartilage products on the development of blood vessels in the chorioallantoic membrane of chicken embryos, the cornea of rabbits, or the conjunctiva of mice.[26-28,32,35,38,40,42,44,46,48]

In human studies (MDA-ID-99303, AETERNA-AE-MM-00-02, and NCCTG-971151), cartilage products...
have been administered topically or orally, or they have been given by enema or subcutaneous injection.[2-4,7-9] AETERNA-AE-RC-99-02,[6,15,16,18,60] For oral administration, liquid, powdered, and pill forms have been used as described in the following closed trials, MDA-ID-99303, NCCTG-971151, and AETERNA-AE-MM-00-02.[2-4,6-9,15,16,18] The dose and duration of cartilage treatment have varied in human studies, in part because different types of products have been tested.

In this summary, the brand name (i.e., registered or trademarked name) of the cartilage product(s) used in individual studies will be identified wherever possible.

References


24. Durie BG, Soehnlen B, Prudden JF: Antitumor activity of bovine cartilage extract (Catrix-S) in


History

The therapeutic potential of cartilage has been investigated for more than 30 years. As noted previously (refer to the General Information section of this summary for more information), cartilage products have been tested as treatments for people with cancer, psoriasis, and arthritis. Cartilage products have also been studied as enhancers of wound repair and as treatments for people with osteoporosis, ulcerative colitis, regional enteritis, acne, scleroderma, hemorrhoids, severe anal itching, and the dermatitis caused by poison oak and poison ivy. [1-5]
Early studies of cartilage’s therapeutic potential utilized extracts of bovine (cow) cartilage. The ability of these extracts to suppress inflammation was first described in the early 1960s.[1] The first report that bovine cartilage contains at least one angiogenesis inhibitor was published in the mid-1970s.[6] The use of bovine cartilage extracts to treat patients with cancer and the ability of these extracts to kill cancer cells directly and to stimulate animal immune systems were first described in the mid- to late-1980s.[7-10]

The first report that shark cartilage contains at least one angiogenesis inhibitor was published in the early 1980s,[11] and the only published report to date of a clinical trial of shark cartilage as a treatment for people with cancer appeared in the late 1990s.[12] The more recent interest in shark cartilage is due, in part, to the greater abundance of cartilage in this animal and its apparently higher level of antiangiogenic activity. Approximately 6% of the body weight of a shark is composed of cartilage, compared with less than 1% of the body weight of a cow.[13] In addition, on a weight-for-weight basis, shark cartilage contains approximately 1,000 times more antiangiogenic activity than bovine cartilage.[11]

As indicated previously (refer to the Overview and General Information sections of this summary for more information), at least three different mechanisms of action have been proposed to explain the anticancer potential of cartilage: 1) it is toxic to cancer cells; 2) it stimulates the immune system; and 3) it inhibits angiogenesis. Only limited evidence is available to support the first two mechanisms of action; however, the evidence in favor of the third mechanism is more substantial (refer to the Laboratory/Animal/Preclinical Studies section of this summary for more information).

The process of angiogenesis requires at least four coordinated steps, each of which may be a target for inhibition. First, tumors must communicate with the endothelial cells that line the inside of nearby blood vessels. This communication takes place, in part, through the secretion of angiogenesis factors such as vascular endothelial growth factor.[14-18] Second, the activated endothelial cells must divide to produce new endothelial cells, which will be used to make the new blood vessels.[15,17-20] Third, the dividing endothelial cells must migrate toward the tumor.[15-20] To accomplish this, they must produce enzymes called matrix metalloproteinases, which will help them carve a pathway through the tissue elements that separate them from the tumor.[18-22] Fourth, the new endothelial cells must form the hollow tubes that will become the new blood vessels.[17,18] Some angiogenesis inhibitors may be able to block more than one step in this process.

Cartilage is relatively resistant to invasion by tumor cells,[23-30] and tumor cells use matrix metalloproteinases when they migrate during the process of metastasis.[21,25,31,32] Therefore, if the angiogenesis inhibitors in cartilage are also inhibitors of matrix metalloproteinases, then the
same molecules may be able to block both angiogenesis and metastasis. Shark tissues other than cartilage have also been reported to produce antitumor substances.[33-36]

References


Laboratory/Animal/Preclinical Studies

The antitumor potential of cartilage has been investigated extensively in laboratory and animal studies. Some of these studies have assessed the toxicity of cartilage products toward cancer cells in vitro.[1-5]

Powdered Cartilage Products

In one study, cells from 22 freshly isolated human tumors (nine ovary, three lung, two brain, two
breast, and one each of sarcoma, melanoma, colon, pancreas, cervix, and testis) and three human cultured cell lines (breast cancer, colon cancer, and myeloma) were treated with Catrix, which is a commercially available powdered preparation of bovine (cow) cartilage.[1,3,4] In the study, the growth of all three cultured cell lines and cells from approximately 70% of the tumor specimens were inhibited by 50% or more when Catrix was used at high concentrations (1–5 mg/mL of culture fluid). However, it is unclear whether the inhibitory effect of Catrix in this study was specific to the growth of cancer cells because the preparation’s effect on the growth of normal cells was not tested. In addition, the cytotoxic component of Catrix has not been identified, and it has not been shown that equivalent inhibitory concentrations of this component can be achieved in the bloodstream of patients who may be treated with either injected or oral formulations of this product. (Refer to the Human/Clinical Studies section of this summary for more information.)

A commercially available preparation of powdered shark cartilage (no brand name given) was reported to have no effect on the growth of human astrocytoma cells in vitro.[2] The shark cartilage product tested in this study, however, was examined at only one concentration (0.75 mg/mL).[2]

The immune system–stimulating potential of cartilage has also been investigated in laboratory and animal studies.[6] In one study, Catrix was shown to stimulate the production of antibodies by mouse B cells (B lymphocytes) both in vitro and in vivo. However, increased antibody production in vivo was observed only when Catrix was administered by intraperitoneal or intravenous injection. It was not observed when oral formulations of Catrix were used.[6] In most experiments, the proliferation of mouse B cells (i.e., normal, nonmalignant cells) in vitro was increasingly inhibited as the concentration of Catrix was increased (tested concentration range, 1–20 mg/mL). Catrix has also been reported to stimulate the activity of mouse macrophages in vivo,[3] but results demonstrating this effect have not been published.

The effects of shark cartilage on the immune system were also reported in two studies that used the same purified protein fraction that had exhibited the most immunostimulatory effects when tested.[7,8] One study explored the effects of this fraction on tumor immune response by observing the infiltration of this fraction on CD4 and CD8 lymphocytes in a murine tumor model. An increase in the ratio of CD4/CD8 lymphocytes was seen in tumor-infiltrating lymphocytes but not in peripheral blood lymphocytes.[8] The second study exploring immune system response measured antibody response, cytotoxic assay, lymphocyte transformation, and intratumor T-cell ratio in mice. The fraction exhibited the ability to augment delayed-type hypersensitivity response against sheep red blood cells in mice and to decrease the cytotoxic activity of natural killer cells. In addition, this fraction showed a strong inhibitory effect on human brain microvascular endothelial cell proliferation and migration in the fibrin matrix.[7]

Additional in vivo studies of the antitumor potential of shark cartilage have been published in the
peer-reviewed scientific literature.[9-11] In one study, oral administration of powdered shark cartilage (no brand name given) was shown to inhibit chemically induced angiogenesis in the mesenteric membrane of rats.[9] In another study, oral administration of powdered shark cartilage (no brand name given) was shown to reduce the growth of GS-9L gliosarcomas in rats. [10] It was reported in a third study that oral administration of two powdered shark cartilage products, Sharkilage and MIA Shark Powder, did not inhibit the growth or the metastasis of SCCVII squamous cell carcinomas in mice.[11]

A large number of laboratory and animal studies concerning the antiangiogenic potential of cartilage have been published.[2,9,12-32] Overall, these studies have revealed the presence of at least three angiogenesis inhibitors in bovine cartilage [13,14,16-18,21,23,33] and at least two in shark cartilage.[2,9,25,26]

### Aqueous Extracts of Cartilage

A liquid (i.e., aqueous) extract of shark cartilage called AE-941/Neovastat has also been reported to inhibit the growth of a variety of cancer cell types *in vitro.*[5] These results have not been published in a peer-reviewed scientific journal and are not consistent with other results obtained by the same group of investigators.[27,34]

Three angiogenesis inhibitors in bovine cartilage have been very well characterized.[13,14,16-18,21,23,33] They are relatively small proteins with molecular masses that range from 23,000 to 28,000.[13,14,16,23] These proteins, called cartilage-derived inhibitor (CDI), cartilage-derived antitumor factor (CATF), and cartilage-derived collagenase inhibitor (CDCI) by the researchers who purified them,[13,14,21] have been shown to block endothelial cell proliferation *in vitro* and new blood vessel formation in the chorioallantoic membrane of chicken embryos.[14,16-18,21,23,33] Two of the proteins (CDI and CDCI) have been shown to inhibit matrix metalloproteinase activity *in vitro,*[13,14,16,18] and one (CDI) has been shown to inhibit endothelial cell migration *in vitro.*[14,16] These proteins do not block the proliferation of normal cells or of tumor cells *in vitro.*[14,16,17,21,33] When the amino acid sequences of CDI, CATF, and CDCI were determined, it was discovered that they were the same as those of proteins known otherwise as tissue inhibitor of matrix metalloproteinases 1 (TIMP-1), chondromodulin I, and TIMP-2, respectively.[13,14,18,23,33]

A possible fourth angiogenesis inhibitor in bovine cartilage has been purified not from cartilage but from the culture fluid of bovine chondrocytes grown in the laboratory.[15] This inhibitor, which has been named chondrocyte-derived inhibitor (ChDI), is a protein that has a molecular mass of approximately 36,000. It has been reported that ChDI and CDI/TIMP-1 have similar antiangiogenic activities,[15,16,33] but the relationship between these proteins is unclear because
amino acid sequence information for ChDI is not available. Thus, whether CDI/TIMP-1 is a breakdown product of ChDI or whether ChDI is truly the fourth angiogenesis inhibitor identified in bovine cartilage is unknown.

As indicated previously, shark cartilage, like bovine cartilage, contains more than one type of angiogenesis inhibitor. One shark cartilage inhibitor, named U-995, reportedly contains two small proteins, one with a molecular mass of approximately 14,000 and the other with a molecular mass of approximately 10,000.[25] Both proteins have shown antiangiogenic activity when tested individually. The exact relationship between these two proteins and their relationship to the larger bovine angiogenesis inhibitors are not known because amino acid sequence information for U-995 is not available. U-995 has been reported to inhibit endothelial cell proliferation, endothelial cell migration, matrix metalloproteinase activity \textit{in vitro}, and the formation of new blood vessels in the chorioallantoic membrane of chicken embryos.[25] It does not appear to inhibit the proliferation of other types of normal cells or of cancer cells \textit{in vitro}. Intraperitoneal but not oral administration of U-995 has been shown to inhibit the growth of mouse sarcoma-180 tumors implanted subcutaneously on the backs of mice and the formation of lung metastases of mouse B16-F10 melanoma cells injected into the tail veins of mice.[25]

The second angiogenesis inhibitor identified in shark cartilage appears to have been studied independently by three groups of investigators.[2,26,35] This inhibitor, which was named SCF2 by one of the groups,[35] is a proteoglycan that has a molecular mass of about 10,000. Proteoglycans are combinations of glycosaminoglycans and protein.[30] The principal glycosaminoglycan in SCF2 is keratan sulfate.[35] SCF2 has been shown to block endothelial cell proliferation \textit{in vitro},[2,26,35] the formation of new blood vessels in the chorioallantoic membrane of chicken embryos,[2,26] and tumor-induced angiogenesis in the corneas of rabbits.[2,26]

Other studies have demonstrated that AE-941/Neovastat, the previously mentioned aqueous extract of shark cartilage, has antiangiogenic activity,[12,27,28,34,36-39] but the molecular basis for this activity has not been defined. Therefore, whether AE-941/Neovastat contains U-995 and/or SCF2 or some other angiogenesis inhibitor is not known. It has been reported that AE-941/Neovastat inhibits endothelial cell proliferation and matrix metalloproteinase activity \textit{in vitro} and the formation of new blood vessels in the chorioallantoic membrane of chicken embryos.[12,27,31] In addition, AE-941/Neovastat has been shown to induce endothelial cell apoptosis by activating caspases, enzymes important in the promotion and regulation of apoptosis.[32,34,38] It also appears to inhibit the action of vascular endothelial growth factor, thus interfering with the communication between tumor cells and nearby blood vessels.[28,34,37,38] AE-941/Neovastat may also inhibit angiogenesis through promotion of tissue plasminogen activator (tPA) activity. Neovastat stimulates tPA expression in endothelial cells through an increase in the transcription of the tPA gene.[40] This transcriptional activation is associated with activation of c-Jun N-terminal
kinase (JNK) and nuclear factor-kappa B (NF-kappa B) signaling pathways to an extent similar to tumor necrosis factor-alpha (TNF-alpha).[40] Furthermore, AE-941/Neovastat has been reported to inhibit the growth of DA3 mammary adenocarcinoma cells and the metastasis of Lewis lung carcinoma cells \textit{in vivo} in mice.[5,27,34,41] In the Lewis lung carcinoma experiments, AE-941/Neovastat enhanced the antimetastatic effect of the chemotherapy drug cisplatin.[5,27,34,41] All the aspects of preclinical development have been reviewed.[42] The cartilage-derived antiangiogenic substance troponin I (TnI) has been isolated from human cartilage and has been produced by the cloning and expression of cDNA of human cartilage. It has been shown to specifically inhibit angiogenesis \textit{in vivo} and \textit{in vitro} and tumor metastasis \textit{in vivo}.[43] The active site of TnI has been located in the amino acid residues of 96 to 116. The synthetic peptide Glu94-Leu123 (pTnI) has been shown to be a potent inhibitor of endothelial cell tube formation and endothelial cell division and to inhibit pancreatic cancer metastases in an \textit{in vivo} liver metastases model.[44]

**References**


Abstract


Human/Clinical Studies

Since the early 1970s, at least a dozen clinical trials (MDA-ID-99303, NCCTG-971151, and AETERNA-AE-MM-00-02) of cartilage as a treatment for people with cancer have been (or are being) conducted;[1-15] (refer to the table at the end of this section) however, results from only seven studies have been published in peer-reviewed scientific journals.[1,2,4,8,9,16] It is not clear whether any of the patients in these studies were children.

In the first randomized trial published in a peer-reviewed scientific journal, 83 incurable breast cancer and colorectal cancer patients were randomly assigned to receive either shark cartilage or placebo, in addition to standard care. No difference was observed in survival or quality of life
between those receiving shark cartilage and those receiving placebo.[8] Additional clinical studies 
are under way; however, the cumulative evidence to date is inconclusive regarding the 
effectiveness of cartilage as a treatment for people with cancer.

**Powdered Cartilage Products**

Two of the three published clinical studies evaluated the use of Catrix, the previously mentioned 
(refer to the Laboratory/Animal/Preclinical Studies section of this summary for more information) 
powdered preparation of bovine (cow) cartilage, as a treatment for various solid tumors.[1,2] One 
of these studies was a case series that included 31 patients;[1] the other was a phase II clinical 
trial that included 9 patients.[2]

In the case series,[1] all patients were treated with subcutaneously injected and/or oral Catrix; 
however, three patients (one with squamous cell carcinoma of the skin and two with basal cell 
carcinoma of the skin) were also treated with topical preparations. The individual dose, the total 
dose, and the duration of Catrix treatment in this series varied from patient to patient; however, 
the minimum treatment duration was 7 months, and the maximum duration was more than 10 
years. Eighteen patients had been treated with conventional therapy (surgery, chemotherapy, 
radiation therapy, hormonal therapy) within 1 year of the start of Catrix treatment; nine patients 
received conventional therapy concurrently with Catrix treatment; and seven patients received 
conventional therapy both prior to and during Catrix treatment. It was reported that 19 patients 
had a complete response, 10 patients had a partial response, and 1 patient had stable disease 
following Catrix treatment. The remaining patient did not respond to cartilage therapy. Eight of 
the patients with a complete response received no prior or concurrent conventional therapy. 
Approximately half of the patients with a complete response eventually experienced recurrent 
cancer.

This clinical study had several weaknesses that could have affected its outcome, including the 
absence of a control group and the receipt of prior and/or concurrent conventional therapy by 
most patients.

Partial results of a third clinical study of Catrix are described in an abstract submitted for 
presentation at a scientific conference,[3] but complete results of this study have not been 
published in a peer-reviewed scientific journal. In the study, 35 patients with metastatic renal cell 
carcinoma were divided into four groups, and the individuals in each group were treated with 
identical doses of subcutaneously injected and/or oral Catrix. Three partial responses and no 
complete responses were observed among 22 evaluable patients who were treated with Catrix for 
more than 3 months. Following Catrix therapy, 2 of the 22 evaluable patients were reported to 
have stable disease, and 17 were reported to have progressive disease. No relationship between
Catrix dose and tumor response could be established in this study. The third published study of cartilage as a treatment for people with cancer was a phase I/II trial that tested the safety and the efficacy of orally administered Cartilade, a commercially available powdered preparation of shark cartilage, in 60 patients with various types of advanced solid tumors. All but one patient in this trial had been treated previously with conventional therapy. According to the design of the study, no additional anticancer treatment could be given concurrently with Cartilade therapy. No complete responses or partial responses were observed among 50 evaluable patients who were treated with Cartilade for at least 6 weeks. However, stable disease that lasted 12 weeks or more was reported for 10 of the 50 patients. All ten of these patients eventually experienced progressive disease.

Partial results of three other clinical studies of powdered shark cartilage are described in two abstracts submitted for presentation at scientific conferences, but complete results of these studies have not been published in peer-reviewed scientific journals. All three studies were phase II clinical trials that involved patients with advanced disease; two of the studies were conducted by the same group of investigators. These three studies enrolled 20 patients with breast cancer, 12 patients with prostate cancer, and 12 patients with primary brain tumors. All patients had been treated previously with conventional therapy. No other anticancer treatment was allowed concurrently with cartilage therapy. In two of the studies, the name of the cartilage product was not identified; however, in the third study, the commercially available product BeneFin was used. Ten patients in each study completed at least 8 weeks of treatment and therefore were considered evaluable for response. No complete responses or partial responses were observed in any of the studies. Two evaluable patients in the breast cancer study were reported to have stable disease that lasted 8 weeks or more; two evaluable patients in the brain tumor study had stable disease that lasted 20 weeks or more; and three evaluable patients in the prostate cancer study had stable disease that also lasted 20 weeks or more.

Aqueous Extracts of Cartilage

In the phase II trial, Catrix was administered by subcutaneous injection only. All patients in this trial had progressive disease following radiation therapy and/or chemotherapy. Identical individual doses of Catrix were administered to each patient, but the duration of treatment and the total delivered dose varied because of disease progression or death. The minimum duration of Catrix treatment in this study was 4 weeks. One patient (with metastatic renal cell carcinoma) reportedly had a complete response that lasted more than 39 weeks. The remaining eight patients did not respond to Catrix treatment. The researchers in this trial also investigated whether Catrix had an effect on immune system function in these patients. No consistent trend or change in the numbers, percentages, or ratios of white blood cells (i.e., total lymphocyte counts,
total T cell counts, total B cell counts, percentage of T cells, percentage of B cells, and ratio of helper T cells to cytotoxic T cells) was observed, though increased numbers of T cells were found in three patients.

The safety and the efficacy of AE-941/Neovastat, the previously mentioned aqueous extract of shark cartilage, has also been examined in clinical studies.[9-11,15,17] It has been reported that AE-941/Neovastat has little toxicity.[10,11,15] In addition, there is evidence from a randomized clinical trial that examined the effect of AE-941/Neovastat on angiogenesis associated with surgical wound repair that this product contains at least one antiangiogenic component that is orally bioavailable.[17]

AE-941/Neovastat was administered to 331 patients with advanced solid tumors (including lung, prostate, breast, and kidney tumors) in two phase I/II trials.[10] The results of these trials, however, have not been fully reported. A retrospective analysis involving a subgroup of patients with advanced non-small cell lung cancer (NSCLC) suggests that AE-941/Neovastat is able to lengthen the survival of patients with this disease.[10] Furthermore, in a prospective analysis involving 22 patients with refractory renal cell carcinoma, survival was longer in patients treated with 240 mL /day AE-941/Neovastat than in patients treated with only 60 mL/day.[7,10,16]

In 2003, the results of a phase I/II trial of AE-941/Neovastat in 80 patients with advanced NSCLC reported that there was a significant survival advantage for patients receiving the highest doses (2.6 mL/kg/day) of AE-941/Neovastat. A survival analysis of 48 patients with unresectable stage IIIA, IIIB, or IV NSCLC showed a median survival advantage of \( P = .0026 \) in patients receiving the highest doses. The trial was principally conducted to explore the safety and efficacy of orally administered AE-941/Neovastat when administered in escalating doses (30, 60, 120, and 240 mL/day). No dose-limiting toxicity was found, and no tumor response was observed.[9]

In 2001, a phase II trial (AETERNA-AE-MM-00-02) of AE-941/Neovastat was initiated in patients with relapsed or refractory multiple myeloma. This trial closed approximately 1 year later, and no results have been reported.[18]

Two randomized phase III trials of AE-941/Neovastat in patients with advanced cancer have been approved by the U.S. Food and Drug Administration (FDA). In one trial (MDA-ID-99303), which is completed, treatment with oral AE-941/Neovastat plus chemotherapy and radiation therapy was compared with treatment with placebo plus the same chemotherapy and radiation therapy in patients with stage III NSCLC. In the second trial, which closed to patient recruitment in 2002, treatment with oral AE-941/Neovastat was compared with treatment with placebo in patients with metastatic renal cell carcinoma. Results from this second phase III trial have not been reported in the peer-reviewed scientific literature.[19] Despite AE-941/Neovastat being granted orphan drug status by the FDA in 2002 for use in the treatment of renal cell carcinoma, the company that
produces AE-941/Neovastat, Aeterna Laboratories, announced in early 2004 that this application would be discontinued in favor of a focus on the treatment of NSCLC.[19,20]

In 2010, the results of a randomized, double-blind, placebo-controlled phase III trial aimed at assessing the effect of adding AE-941 to chemotherapy and radiation therapy on the overall survival of patients with nonresectable stage III NSCLC were reported. A total of 379 eligible patients received induction chemotherapy followed by concurrent chemotherapy with chest radiation therapy; participating centers used one of two chemotherapy regimens, either carboplatin and paclitaxel, or cisplatin and vinorelbine. No statistically significant difference in overall survival was observed between the group (n = 188) receiving chemotherapy and radiation therapy plus AE-941 (120 mL administered orally twice daily) and the group receiving chemotherapy and radiation therapy plus placebo (n = 191). Both AE-941 and placebo were well tolerated.[21]

Cartilage Use in Cancer Treatment: Clinical Studies With Therapeutic Endpoints

<table>
<thead>
<tr>
<th>Reference Citation(s)</th>
<th>Type of Study</th>
<th>Type(s) of Cancer</th>
<th>Car</th>
<th>Therapeutic Endpoints</th>
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<tr>
<td>[8]</td>
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<td>Breast and colorectal</td>
<td>BeneFin (shark)</td>
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<td>NSCLC</td>
<td>AE-941 (shark)</td>
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<td>Catrix (bovine)</td>
<td></td>
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<tr>
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<td>Phase II trial</td>
<td>Various metastatic</td>
<td>Catrix (bovine)</td>
<td></td>
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<tr>
<td>[3]</td>
<td>Phase II trial</td>
<td>Metastatic renal cell</td>
<td>Catrix (bovine)</td>
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<tr>
<td>Reference</td>
<td>Trial Type</td>
<td>Indication</td>
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<td>[10,16]</td>
<td>Two phase I/II trials⁹</td>
<td>Various advanced, refractory solid tumors</td>
<td>AE-941/Neovastat (shark)</td>
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<tr>
<td>[9]</td>
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<td>Cartilage (shark)</td>
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<td>[5]</td>
<td>Phase II trial</td>
<td>Metastatic, hormone-refractory prostate</td>
<td>Unknown (shark)</td>
<td></td>
</tr>
</tbody>
</table>
No. = number; NSCLC = non-small cell lung cancer; wk = week.

See text and the NCI Dictionary of Cancer Terms for additional information and definition of terms.

Other clinical studies have been conducted, but no results have been reported.

Strongest evidence reported that the treatment under study has anticancer activity or otherwise improves the well-being of cancer patients.

Chemotherapy, radiation therapy, hormonal therapy, or cytokine therapy given/allowed at the same time as cartilage therapy.

For information about Levels of Evidence analysis and an explanation of the level of evidence scores, see Levels of Evidence for Human Studies of Cancer Complementary and Alternative Medicine.

Study results reported in review article or abstract form only; insufficient information presented for Level of Evidence analysis.

Insufficient information available to describe these studies separately.

References


Adverse Effects

The side effects associated with cartilage therapy are generally described as mild to moderate in severity. Inflammation at injection sites, dysgeusia, fatigue, nausea, dyspepsia, fever, dizziness, and edema of the scrotum have been reported after treatment with the bovine (cow) cartilage product Catrix.[1-3] Nausea, vomiting, abdominal cramping and/or bloating, constipation, hypotension, hyperglycemia, generalized weakness, and hypercalcemia have been associated with the use of powdered shark cartilage.[4-6] The high level of calcium in shark cartilage may contribute to the development of hypercalcemia.[5,7] In addition, one case of hepatitis has been associated with the use of powdered shark cartilage.[8] Nausea, vomiting, and dyspepsia are the most commonly reported side effects following treatment with AE-941/Neovastat, the aqueous extract of shark cartilage.[9]

References


**Summary of the Evidence for Cartilage**

Although at least a dozen clinical studies of cartilage as a treatment for people with cancer have been conducted since the early 1970s, relatively few results have been reported in the peer-reviewed scientific literature. There are small amounts of reported data from phase III clinical trials. Additional clinical studies are now under way. At present, the use of cartilage (bovine [cow] or shark) as a treatment for people with cancer cannot be recommended outside the context of well-designed clinical trials.

Separate levels of evidence scores are assigned to qualifying human studies on the basis of statistical strength of the study design and scientific strength of the treatment outcomes (i.e., endpoints) measured. The resulting two scores are then combined to produce an overall score. For additional information about levels of evidence analysis, refer to Levels of Evidence for Human Studies of Cancer Complementary and Alternative Medicine.

**Changes to This Summary (05/21/2015)**

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

**Overview**

Added text to note that the information in this summary is no longer being updated and is provided for reference purposes only.

This summary is written and maintained by the PDQ Cancer Complementary and Alternative Medicine Editorial Board, which is editorially independent of NCI. The summary reflects an independent review of the literature and does not represent a policy statement of NCI or NIH. More information about summary policies and the role of the PDQ Editorial Boards in maintaining the PDQ summaries can be found on the About This PDQ Summary and PDQ NCI's Comprehensive Cancer Database pages.
About This PDQ Summary

Purpose of This Summary
This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the use of cartilage (bovine and shark) in the treatment of people with cancer. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.

Reviewers and Updates
This summary is reviewed regularly and updated as necessary by the PDQ Cancer Complementary and Alternative Medicine Editorial Board, which is editorially independent of the National Cancer Institute (NCI). The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH).

Board members review recently published articles each month to determine whether an article should:
- be discussed at a meeting,
- be cited with text, or
- replace or update an existing article that is already cited.

Changes to the summaries are made through a consensus process in which Board members evaluate the strength of the evidence in the published articles and determine how the article should be included in the summary.

The lead reviewers for Cartilage (Bovine and Shark) are:
- John A. Beutler, PhD (National Cancer Institute)
- Keith I. Block, MD (Block Center for Integrative Cancer Treatment & University of Illinois College of Medicine)

Any comments or questions about the summary content should be submitted to Cancer.gov through the Web site's Contact Form. Do not contact the individual Board Members with questions or comments about the summaries. Board members will not respond to individual inquiries.
Levels of Evidence

Some of the reference citations in this summary are accompanied by a level-of-evidence designation. These designations are intended to help readers assess the strength of the evidence supporting the use of specific interventions or approaches. The PDQ Cancer Complementary and Alternative Medicine Editorial Board uses a formal evidence ranking system in developing its level-of-evidence designations.

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Updated: May 21, 2015

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Coenzyme Q10–for health professionals (PDQ®)

Overview

This complementary and alternative medicine (CAM) information summary provides an overview of the use of coenzyme Q10 in cancer therapy. The summary includes a history of coenzyme Q10 research, a review of laboratory studies, and data from investigations involving human subjects. Although several naturally occurring forms of coenzyme Q have been identified, Q10 is the predominant form found in humans and most mammals, and it is the form most studied for therapeutic potential. Thus, it will be the only form of coenzyme Q discussed in this summary.

This summary contains the following key information:

- Coenzyme Q10 is made naturally by the human body.
- Coenzyme Q10 helps cells to produce energy, and it acts as an antioxidant.
- Coenzyme Q10 has shown an ability to stimulate the immune system and to protect the heart from damage caused by certain chemotherapy drugs.
- Low blood levels of coenzyme Q10 have been detected in patients with some types of cancer.
- No report of a randomized clinical trial of coenzyme Q10 as a treatment for cancer has been published in a peer-reviewed scientific journal.
- Coenzyme Q10 is marketed in the United States as a dietary supplement.

Many of the medical and scientific terms used in the summary are hypertext linked (at first use in each section) to the NCI Dictionary of Cancer Terms, which is oriented toward nonexperts. When a linked term is clicked, a definition will appear in a separate window.

Reference citations in some PDQ CAM information summaries may include links to external Web sites that are operated by individuals or organizations for the purpose of marketing or advocating the use of specific treatments or products. These reference citations are included for informational purposes only. Their inclusion should not be viewed as an endorsement of the content of the Web sites, or of any treatment or product, by the PDQ Cancer CAM Editorial Board or the National Cancer Institute.
General Information

Coenzyme Q10 (also known as CoQ10, Q10, vitamin Q10, ubiquinone, and ubidecarenone) is a benzoquinone compound synthesized naturally by the human body. The “Q” and the “10” in the name refer to the quinone chemical group and the 10 isoprenyl subunits that are part of this compound’s structure. The term “coenzyme” denotes it as an organic (contains carbon atoms), nonprotein molecule necessary for the proper functioning of its protein partner (an enzyme or an enzyme complex). Coenzyme Q10 is used by cells of the body in a process known variously as aerobic respiration, aerobic metabolism, oxidative metabolism, or cell respiration. Through this process, mitochondria produce energy for cell growth and maintenance.[1-4] Coenzyme Q10 is also used by the body as an endogenous antioxidant.[1,2,4-8] An antioxidant is a substance that protects cells from free radicals, which are highly reactive chemicals, often containing oxygen atoms, capable of damaging important cellular components such as DNA and lipids. In addition, the plasma level of coenzyme Q10 has been used in studies as a measure of oxidative stress. [9,10]

Coenzyme Q10 is present in most tissues, but the highest concentrations are found in the heart, the liver, the kidneys, and the pancreas.[11] The lowest concentration is found in the lungs.[11] Tissue levels of this compound decrease as people age, due to increased requirements, decreased production,[11] or insufficient intake of the chemical precursors needed for synthesis. [12] In humans, normal blood levels of coenzyme Q10 have been defined variably, with reported normal values ranging from 0.30 to 3.84 µg /mL.[2,4,13,14]

Given the importance of coenzyme Q10 in optimizing cellular energy production, use of this compound as a treatment for diseases other than cancer has been explored. Most of these investigations have focused on coenzyme Q10 as a treatment for cardiovascular disease.[2,4,15] In patients with cancer, coenzyme Q10 has been shown to protect the heart from anthracycline-induced cardiotoxicity (anthracyclines are a family of chemotherapy drugs, including doxorubicin, that have the potential to damage the heart)[3,16-18] and to stimulate the immune system. [19,20] Stimulation of the immune system by this compound has also been observed in animal studies and in humans without cancer.[21-27] In part because of its immunostimulatory potential, coenzyme Q10 has been used as an adjuvant therapy in patients with various types of cancer. [17,20,28-33]

While coenzyme Q10 may show indirect anticancer activity through its effect(s) on the immune system, there is evidence to suggest that analogs of this compound can suppress cancer growth directly. Analogs of coenzyme Q10 have been shown to inhibit the proliferation of cancer cells in vitro and the growth of cancer cells transplanted into rats and mice.[12,34] In view of these findings, it has been proposed that analogs of coenzyme Q10 may function as antimetabolites to
disrupt normal biochemical reactions that are required for cell growth and/or survival and, thus, that they may be useful as chemotherapeutic agents.[12,34]

Several companies distribute coenzyme Q10 as a dietary supplement. In the United States, dietary supplements are regulated as foods, not drugs. Therefore, premarket evaluation and approval by the U.S. Food and Drug Administration (FDA) are not required unless specific disease prevention or treatment claims are made. The FDA can, however, remove from the market dietary supplements that it deems unsafe. Because dietary supplements are not formally reviewed for manufacturing consistency, there may be considerable variation from lot to lot. The FDA has not approved coenzyme Q10 for the treatment of cancer or any other medical condition.

To conduct clinical drug research in the United States, researchers must file an Investigational New Drug (IND) application with the FDA. The IND application process is highly confidential, and IND information can be disclosed only by the applicants. To date, no investigators have announced that they have applied for an IND to study coenzyme Q10 as a treatment for cancer.

In animal studies, coenzyme Q10 has been administered by injection (intravenous, intraperitoneal, intramuscular, or subcutaneous). In humans, it is usually taken orally as a pill (gel bead or capsule), but intravenous infusions have been given.[4] Coenzyme Q10 is absorbed best with fat; therefore, lipid preparations are better absorbed than the purified compound.[2,4] In human studies, supplementation doses and administration schedules have varied, but usually have been in the range of 90 to 390 mg/day.

References


History

Coenzyme Q10 was first isolated in 1957, and its chemical structure (benzoquinone compound) was determined in 1958.[1,2] Interest in coenzyme Q10 as a therapeutic agent in cancer began in 1961, when a deficiency was noted in the blood of both Swedish and American cancer patients, especially in the blood of patients with breast cancer.[2-4] A subsequent study showed a statistically significant relationship between the level of plasma coenzyme Q10 deficiency and breast cancer prognosis.[5] Low blood levels of this compound have been reported in patients with malignancies other than breast cancer, including myeloma, lymphoma, and cancers of the lung, prostate, pancreas, colon, kidney, and head and neck.[2,6,7] Furthermore, decreased levels of coenzyme Q10 have been detected in malignant human tissue,[8-12] but increased levels have been reported as well.[8]

A large amount of laboratory and animal data on coenzyme Q10 have accumulated since 1962.[2] Research into cellular energy-producing mechanisms that involve this compound was awarded the Nobel Prize in Chemistry in 1978. Some of the accumulated data show that coenzyme Q10 stimulates animal immune systems, leading to higher antibody levels,[13] greater numbers and/or activities of macrophages and T cells (T lymphocytes),[13,14] and increased resistance to infection.[15-17] Coenzyme Q10 has also been reported to increase IgG (immunoglobulin G) antibody levels and to increase the CD4 to CD8 T-cell ratio in humans.[18-20] CD4 and CD8 are proteins found on the surface of T cells, with CD4 and CD8 identifying helper T cells and cytotoxic T cells, respectively; decreased CD4 to CD8 T-cell ratios have been reported for cancer patients.[21,22] Research subsequently delineated the antioxidant properties of coenzyme Q10.[23-27]

Proposed mechanisms of action for coenzyme Q10 that are relevant to cancer include its essential function in cellular energy production and its stimulation of the immune system (which may both be related), as well as its role as an antioxidant. Coenzyme Q10 is essential to aerobic energy production,[1,25,28] and it has been suggested that increased cellular energy leads to increased antibody synthesis in B cells (B lymphocytes).[6,18] As noted previously (General Information section), coenzyme Q10 can also behave as an antioxidant.[1,25-27,29-32] In this capacity,
Coenzyme Q10 is thought to stabilize cell membranes (lipid-containing structures essential to maintaining cell integrity) and to prevent free radical damage to other important cellular components.[1,25,27,32] Free radical damage to DNA (and possibly to other cellular molecules) may be a factor in cancer development.[11,23,30,33-36]

References

1996. [PUBMED Abstract]


Laboratory/Animal/Preclinical Studies

Laboratory work on coenzyme Q10 has focused primarily on its structure and its function in cell
respiration. Studies in animals have demonstrated that coenzyme Q10 is capable of stimulating the immune system, with treated animals showing increased resistance to protozoal infections [1,2] and to viral and chemically-induced neoplasia.[1-4] Early studies of coenzyme Q10 showed increased hematopoiesis (the formation of new blood cells) in monkeys,[4,5] rabbits,[6] and poultry.[5] Coenzyme Q10 demonstrated a protective effect on the heart muscle of mice, rats, and rabbits given the anthracycline anticancer drug doxorubicin.[7-12] Although another study confirmed this protective effect with intraperitoneal administration of doxorubicin in mice, it failed to demonstrate a protective effect when the anthracycline was given intravenously, which is the route of administration in humans.[13] Researchers in one study sounded a cautionary note when they found that coadministration of coenzyme Q10 and radiation therapy decreased the effectiveness of the radiation therapy.[14] In this study, mice inoculated with human small cell lung cancer cells (a xenograft study), and then given coenzyme Q10 and single-dose radiation therapy, showed substantially less inhibition of tumor growth than mice in the control group that were treated with radiation therapy alone. Since radiation leads to the production of free radicals, and since antioxidants protect against free radical damage, the effect in this study might be explained by coenzyme Q10 acting as an antioxidant. As noted previously (General Information), there is some evidence from laboratory and animal studies that analogs of coenzyme Q10 may have direct anticancer activity.[15,16]

References


Human/Clinical Studies

The use of coenzyme Q10 as a treatment for cancer in humans has been investigated in only a limited manner. The studies that have been published consist of randomized controlled trials, anecdotal reports, case reports, case series, and uncontrolled clinical studies.[1-12]
In view of the promising results from animal studies, coenzyme Q10 was tested as a protective agent against the cardiac toxicity observed in cancer patients treated with the anthracycline drug doxorubicin. It has been postulated that doxorubicin interferes with energy-generating biochemical reactions that involve coenzyme Q10 in heart muscle mitochondria and that this interference can be overcome by coenzyme Q10 supplementation.\cite{2,13,14} Studies with adults and children, including the aforementioned randomized trial, have confirmed the decrease in cardiac toxicity observed in animal studies.\cite{1-3,7} A randomized trial \cite{7} of 20 patients tested the ability of coenzyme Q10 to reduce cardiotoxicity caused by anthracycline drugs.

A larger randomized, placebo-controlled trial of 236 breast cancer patients concluded that coenzyme Q10 at a daily dose of 300 mg combined with 300 IU of vitamin E, divided into three doses, did not improve fatigue levels or quality of life after 24 weeks of supplementation.\cite{8}

The potential of coenzyme Q10 as an adjuvant therapy for cancer has also been explored. In view of observations that blood levels of coenzyme Q10 are frequently reduced in cancer patients, \cite{6,10,11,15,16} supplementation with this compound has been tested in patients undergoing conventional treatment. An open-label (nonblinded), uncontrolled clinical study in Denmark followed 32 breast cancer patients for 18 months.\cite{4} The disease in these patients had spread to the axillary lymph nodes, and an unreported number had distant metastases. The patients received antioxidant supplementation (vitamin C, vitamin E, and beta carotene), other vitamins and trace minerals, essential fatty acids, and coenzyme Q10 (at a dose of 90 mg/day), in addition to standard therapy (surgery, radiation therapy, and chemotherapy, with or without tamoxifen). The patients were seen every 3 months to monitor disease status (progressive disease or recurrence), and, if there was a suspicion of recurrence, mammography, bone scan, x-ray, or biopsy was performed. The survival rate for the study period was 100\% (4 deaths were expected). Six patients were reported to show some evidence of remission; however, incomplete clinical data were provided, and information suggestive of remission was presented for only 3 of the 6 patients. None of the 6 patients had evidence of further metastases. For all 32 patients, decreased use of painkillers, improved quality of life, and an absence of weight loss were reported. Whether painkiller use and quality of life were measured objectively (e.g., from pharmacy records and validated questionnaires, respectively) or subjectively (from patient self-reports) was not specified.

In a follow-up study, 1 of the 6 patients with a reported remission and a new patient were treated for several months with higher doses of coenzyme Q10 (390 and 300 mg/day, respectively).\cite{5} Surgical removal of the primary breast tumor in both patients had been incomplete. After 3 to 4 months of high-level coenzyme Q10 supplementation, both patients appeared to experience complete regression of their residual breast tumors (assessed by clinical examination and mammography). It should be noted that a different patient identifier was used in the follow-up...
study for the patient who had participated in the original study. Therefore, it is impossible to determine which of the 6 patients with a reported remission took part in the follow-up study. In the follow-up study report, the researchers noted that all 32 patients from the original study remained alive at 24 months of observation, whereas 6 deaths had been expected.[5]

In another report by the same investigators, 3 breast cancer patients were followed for a total of 3 to 5 years on high-dose coenzyme Q10 (390 mg/day).[6] One patient had complete remission of liver metastases (determined by clinical examination and ultrasonography), another had remission of a tumor that had spread to the chest wall (determined by clinical examination and chest x-ray), and the third patient had no microscopic evidence of remaining tumor after a mastectomy (determined by biopsy of the tumor bed).

All 3 of the above-mentioned human studies [4-6] had important design flaws that could have influenced their outcome. Study weaknesses include the absence of a control group (i.e., all patients received coenzyme Q10), possible selection bias in the follow-up investigations, and multiple confounding variables (i.e., the patients received a variety of supplements in addition to coenzyme Q10, and they received standard therapy either during or immediately before supplementation with coenzyme Q10). Thus, it is impossible to determine whether any of the beneficial results was directly related to coenzyme Q10 therapy.

Anecdotal reports of coenzyme Q10 lengthening the survival of patients with pancreatic, lung, rectal, laryngeal, colon, and prostate cancers also exist in the peer-reviewed scientific literature. [3] The patients described in these reports also received therapies other than coenzyme Q10, including chemotherapy, radiation therapy, and surgery.

**Current Clinical Trials**

Check NCI’s list of cancer clinical trials for cancer CAM clinical trials on coenzyme Q10 that are actively enrolling patients.

General information about clinical trials is also available from the NCI Web site.

**References**


**Adverse Effects**

No serious toxicity associated with the use of coenzyme Q10 has been reported.[1-4] Doses of 100 mg /day or higher have caused mild insomnia in some individuals. Liver enzyme elevation has been detected in patients taking doses of 300 mg/day for extended periods of time, but no liver toxicity has been reported.[1] Researchers in one cardiovascular study reported that coenzyme Q10 caused rashes, nausea, and epigastric (upper abdominal) pain that required withdrawal of a small number of patients from the study.[5] Other reported side effects have included dizziness, photophobia (abnormal visual sensitivity to light), irritability,[5] headache, heartburn, and fatigue. [6]

Certain lipid-lowering drugs, such as the statins (lovastatin, pravastatin, and simvastatin) and gemfibrozil, as well as oral agents that lower blood sugar, such as glyburide and tolazamide, cause a decrease in serum levels of coenzyme Q10 and reduce the effects of coenzyme Q10 supplementation.[1,7-9] Beta-blockers (drugs that slow the heart rate and lower blood pressure) can inhibit coenzyme Q10-dependent enzyme reactions. The contractile force of the heart in patients with high blood pressure can be increased by coenzyme Q10 administration.[1] Coenzyme Q10 can reduce the body’s response to the anticoagulant drug warfarin.[9] Finally, coenzyme Q10 can decrease insulin requirements in individuals with diabetes.

**References**

Summary of the Evidence for Coenzyme Q10

To assist readers in evaluating the results of human studies of complementary and alternative medicine (CAM) treatments for cancer, the strength of the evidence (i.e., the “levels of evidence”) associated with each type of treatment is provided whenever possible. To qualify for a level of evidence analysis, a study must:

- Be published in a peer-reviewed scientific journal.
- Report on a therapeutic outcome or outcomes, such as tumor response, improvement in survival, or measured improvement in quality of life.
- Describe clinical findings in sufficient detail that a meaningful evaluation can be made.

Separate levels of evidence scores are assigned to qualifying human studies on the basis of statistical strength of the study design and scientific strength of the treatment outcomes (i.e., endpoints) measured. The resulting two scores are then combined to produce an overall score. A table showing the levels of evidence scores for qualifying human studies cited in this summary is presented below. For an explanation of the scores and additional information about levels of evidence analysis of CAM treatments for cancer, refer to Levels of Evidence for Human Studies of Cancer Complementary and Alternative Medicine.

Coenzyme Q10 Summary: Reference Numbers and the Corresponding Levels of Evidence
References


Changes to This Summary (05/14/2014)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

Editorial changes were made to this summary.

This summary is written and maintained by the PDQ Cancer Complementary and Alternative Medicine Editorial Board, which is editorially independent of NCI. The summary reflects an independent review of the literature and does not represent a policy statement of NCI or NIH. More information about summary policies and the role of the PDQ Editorial Boards in maintaining the PDQ summaries can be found on the About This PDQ Summary and PDQ NCI's Comprehensive Cancer Database pages.

About This PDQ Summary

Purpose of This Summary

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the use of coenzyme Q10 in the treatment of people with cancer. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.

Reviewers and Updates
This summary is reviewed regularly and updated as necessary by the PDQ Cancer Complementary and Alternative Medicine Editorial Board, which is editorially independent of the National Cancer Institute (NCI). The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH).

Board members review recently published articles each month to determine whether an article should:

- be discussed at a meeting,
- be cited with text, or
- replace or update an existing article that is already cited.

Changes to the summaries are made through a consensus process in which Board members evaluate the strength of the evidence in the published articles and determine how the article should be included in the summary.

The lead reviewer for Coenzyme Q10 is:

- Jeffrey D. White, MD (National Cancer Institute)

Any comments or questions about the summary content should be submitted to Cancer.gov through the Web site's Contact Form. Do not contact the individual Board Members with questions or comments about the summaries. Board members will not respond to individual inquiries.

Levels of Evidence

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Milk Thistle–for health professionals (PDQ®)

Overview

This complementary and alternative medicine (CAM) information summary provides an overview of the use of milk thistle as a treatment and adjunct agent for people with cancer.

The summary includes a brief history of milk thistle, a review of the laboratory studies and clinical trials, and a description of adverse effects associated with milk thistle use.

This summary contains the following key information:

• Milk thistle is a plant whose fruit and seeds have been used for more than 2,000 years as a treatment for liver and biliary disorders.

• The active substance in milk thistle, silymarin, is a complex mixture of flavonolignans, primarily consisting of the following isomers: silybin (consisting of silybins A and B), isosilybin (consisting of isosilybins A and B), silychristin (also known as silichristin), and silydianin (also known as silidianin). In the literature, silybin is often referred to as silibinin.

• Laboratory studies demonstrate that silymarin functions as an antioxidant, stabilizes cellular membranes, stimulates detoxification pathways, stimulates regeneration of liver tissue, inhibits the growth of certain cancer cell lines, exerts direct cytotoxic activity toward certain cancer cell lines, and may increase the efficacy of certain chemotherapy agents.

• Human clinical trials have investigated milk thistle or silymarin primarily in individuals with hepatitis or cirrhosis.

• Few adverse side effects have been reported for milk thistle, but little information about interactions with anticancer medications or other drugs is available.

• Milk thistle is available in the United States as a dietary supplement.

Many of the medical and scientific terms used in the summary are hypertext linked (at first use in each section) to the NCI Dictionary of Cancer Terms, which is oriented toward nonexperts. When a linked term is clicked, a definition will appear in a separate window.

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the use of specific treatments or products. These reference citations are included for informational purposes only. Their inclusion should not be viewed as an endorsement of the content of the Web sites, or of any treatment or product, by the PDQ Cancer CAM Editorial Board or the National Cancer Institute.

General Information

The botanical name for milk thistle is *Silybum marianum* (L.) Gaertn. Milk thistle is also referred to as holy thistle, Marian thistle, Mary thistle, Our Lady’s thistle, St. Mary thistle, wild artichoke, Mariendistel (German), and Chardon-Marie (French). The plant is indigenous to Europe but can also be found in the United States and South America. Traditionally, the leaves have been used in salads, and the fruit of the flower has been roasted as a coffee substitute. The seeds of milk thistle are the medicinal parts of the plant.[1] The primary active constituent of milk thistle is silymarin, which is composed of the following isomers: silybin (consisting of silybins A and B), isosilybin (consisting of isosilybins A and B), silychristin, and silydianin. Most supplements are standardized according to their silybin content. Silybin and isosilybin are both mixtures of two diastereomers, silybins A and B and isosilybins A and B, respectively.[2,3] Special formulations of silybin have been developed to enhance the bioavailability of the herbal product; these forms are sold under the names Legalon, silipide, and Siliphos. Because of milk thistle’s lipophilic nature, it is usually administered in capsule or tablet form rather than as an herbal tea. In Europe, silybin is administered intravenously as the only effective antidote for *Amanita phalloides* (Fr.).[4] Humans exposed to this mushroom toxin develop serious liver failure that ultimately progresses to death.

Several companies distribute milk thistle as a dietary supplement. In the United States, dietary supplements are regulated as foods, not drugs. Therefore, premarket evaluation and approval by the Food and Drug Administration (FDA) are not required unless specific disease prevention or treatment claims are made. Because dietary supplements are not formally reviewed for manufacturing consistency, ingredients may vary considerably from lot to lot; in addition, there is no guarantee that ingredients identified on product labels are present at all or are present in the specified amounts. It is important to note that the FDA has not approved the use of milk thistle as a treatment for cancer patients or patients with any other medical condition.

To conduct clinical drug research in the United States, researchers must file an Investigational New Drug (IND) application with the FDA. The IND application process is confidential, and IND information can be disclosed only by the applicants. To date, only one investigator has announced holding an IND to study milk thistle as an adjunct cancer treatment.

Despite milk thistle’s long history of being used to treat liver and biliary complaints, it was not until 1968 that silymarin was isolated from the seeds of the plant, and it was proposed that
Silymarin might be the active ingredient. Silymarin was later determined to be a flavonolignan that is composed of four structurally similar compounds: silybin, isosilybin, silydianin, and silychristin. Researchers have investigated the role that silibinin may play in the treatment of hepatitis and cirrhosis. Most studies have investigated the isolated compound silymarin or its most active isomer silybin, rather than the herbal plant in its whole form.

Silymarin is most well known for its purported effects on the liver. In laboratory studies, silymarin has been found to stabilize cell membranes, thus preventing toxic chemicals from entering the cell. Laboratory studies have also demonstrated that silymarin stimulates synthesis and activity of enzymes responsible for detoxification pathways and exhibits antioxidant properties. Specifically, silymarin has been shown to stimulate the glutathione S-transferase pathway and alter the intracellular concentration of glutathione (a potent antioxidant). Silymarin has also been shown to neutralize a wide range of free radicals.

Laboratory experiments conducted using cancer cell lines have suggested that silibinin enhances the efficacy of cisplatin and doxorubicin against ovarian and breast cancer cells. Silybin appears to have direct anticancer effects against prostate, breast, and ectocervical tumor cells. Silybin may also affect the cell cycle in cancer cells by slowing down cell growth, as demonstrated with prostate cancer cell lines. Laboratory studies using leukemia cell lines found that silybin did not stimulate growth of leukemia cells.

No human clinical trials on milk thistle or silymarin as a cancer treatment or as an adjunctive therapy in individuals with cancer have been published. Most clinical trials have investigated silymarin’s effectiveness in the treatment of patients with hepatitis, cirrhosis, or biliary disorders. These studies have employed a wide range of doses (120-560 mg/day) and have yielded conflicting results. Many of the well-designed, large-scale trials have reported a beneficial effect rather than no effect. The most commonly reported adverse effects are a mild laxative effect and gastrointestinal upset.

References


27. Marena C, Lampertico M: Preliminary clinical development of silipide: a new complex of


**History**

Milk thistle has been used for more than 2,000 years, primarily as a treatment for liver dysfunction. The oldest reported use of milk thistle was by Dioscorides, who recommended the herb as a treatment for serpent bites.[1] Pliny the Elder (A.D. 23–79) reported that the juice of the plant mixed with honey is indicated for “carrying off bile.”[1,2] In the Middle Ages, milk thistle was revered as an antidote for liver toxins.[1,2] The British herbalist Culpepper reported it to be effective for relieving obstructions of the liver.[1,2] In 1898, eclectic physicians Felter and Lloyd stated the herb was good for congestion of the liver, spleen, and kidney.[1,2] Native Americans use milk thistle to treat boils and other skin diseases. Homeopathic practitioners used preparations from the seeds to treat jaundice, gallstones, peritonitis, hemorrhage, bronchitis, and varicose veins.[2] The German Commission E recommends milk thistle use for dyspeptic complaints, toxin-induced liver damage, hepatic cirrhosis, and as a supportive therapy for chronic inflammatory liver conditions.[3]

**References**


**Laboratory/Animal/Preclinical Studies**

Research studies conducted in the laboratory have investigated the properties of silymarin or its isomer silybin using cell lines and animal models. Other substances in milk thistle have not been extensively studied.

Several research studies have investigated the effects of silymarin or silybin in a noncancer context. These studies have tested silymarin or silybin:

- In healthy animal liver and kidney cells.
- As a prophylaxis against toxic chemicals.
- In stimulating detoxification pathways (enzyme concentrations and activity).
- For antioxidant properties.

Silymarin or silybin has also been investigated in cancer models. The effects of silymarin and/or silybin have been investigated in prostate (DU 145, LNCaP, PC-3), breast (MDA-MB 468, MCF-7), hepatic (HepG2), epidermoid (A431), colon (Caco-2), ovarian (OVCA 433, A2780), histiocytic lymphoma (U-937), epidermoid (A431), colon (Caco-2), ovarian (OVCA 433, A2780), histiocytic lymphoma (U-937), and leukemia (HL-60) cells. In animal tumor models, tongue cancer, skin cancer, bladder cancer, and adenocarcinoma of the colon and small intestine have been investigated. These studies have tested the ability of silymarin or silibinin to:

- Mitigate the toxicity associated with chemotherapy agents.
- Enhance the efficacy of chemotherapy agents.
- Inhibit the growth of cancer cell lines and inhibit tumor initiation or tumor promotion.

Although many of these studies have produced encouraging results, none of the findings have been replicated in human clinical trials.

Laboratory data suggest that silymarin and silybin protect the liver from damage induced by toxic chemicals. Animal studies have found that liver cells treated with silybin and then exposed to toxins do not incur cell damage or death at the same rate as liver cells that are not treated with silybin. This finding suggests that silybin can prevent toxins from entering the cell or effectively exports toxins out of the cell before damage ensues.[11,27-31] Alternatively, this may be related to the effect of silymarin on detoxification systems. *In vitro* data have shown silybin to stimulate and/or inhibit phase I detoxification pathways in silybin-treated human liver cells. However, this
effect was found to be dose-dependent, and these levels are not physiologically attainable with the current manufacturer dose recommendations.[32,33]

Silymarin has been shown to stimulate phase II detoxification pathways in mice. Administration of silymarin (100 or 200 mg /kg body weight/day) to SENCAR mice for 3 days significantly increased glutathione S-transferase activity in the liver ($P < .01–.001$), lung ($P < .05–.01$), stomach ($P < .05$), small bowel ($P < .01$), and skin ($P < .01$). This effect appeared to be dose-dependent.[34]

Administration of silymarin to rats challenged with a toxin (50 mg/kg body weight) resulted in higher levels of glutathione in liver cells, decreased levels of oxidative stress (measured by malondialdehyde concentrations), and less elevated liver function tests (measured by levels of aspartate aminotransferase [AST] and alanine aminotransferase [ALT]).[31] Silymarin and silybin have also been found to accelerate cell regeneration in the liver through stimulation of precursors to DNA synthesis and enhancement of production of the cellular enzymes required for synthesis of DNA.[35-40] Laboratory studies have also shown silymarin and silybin to be potent antioxidants.[28,29,41-48] Silymarin has been shown to mitigate oxidative stress in cells treated with pro-oxidant compounds.

A number of laboratory studies have investigated the effect of silymarin or silybin on the efficacy and toxicity of chemotherapy agents or have measured their direct cytotoxic activity. In an investigation of the effect of a variety of flavonoids on the formation of DNA damage, silymarin did not induce DNA damage in colon (Caco-2) cells, hepatoma (HepG2) cells, and human lymphocytes.[12] At higher concentrations of silymarin (400–1,000 µmol/L) DNA damage was induced in an epithelial cell line (HeLa cells). At higher concentrations (1,000 µmol/L) DNA damage was observed in human lymphocytes. Cell growth was inhibited as the flavonoid concentration was increased in human lymphocytes and HeLa cells. Only at very high concentrations was cell viability affected by silymarin in HepG2 cells. Although this study demonstrated that the flavonolignans of *Silybum marianum* (L.) are capable of inhibiting cellular proliferation and inducing DNA strand breaks, the results were obtained at very high concentrations that may be difficult to achieve in humans. This study also showed that silymarin does not stimulate cell growth in the HeLa, Burkitt lymphoma, and human hepatoma cell lines.

Silymarin has also been investigated as a possible adjunctive agent in mitigating some of the toxicity associated with chemotherapy agents. Silybin and silychristin exerted a protective effect on monkey kidney cells exposed to vincristine and especially cisplatin chemotherapy.[49] Silybin (200 mg/kg body weight) administration with cisplatin in rats resulted in statistically significant reductions in measures of kidney toxicity.[50] Significant decreases in weight loss, faster recovery of urinary osmolality measures, and depressions in the increase in activity of urinary alanine aminopeptidase ([AAP], a marker of kidney toxicity) were observed. Silybin had no effect on magnesium excretion or glomerular function. Silybin (2 g /kg body weight) administration in rats
receiving cisplatin prevented reductions in creatinine clearance, increases in urea plasma levels, and large increases in urinary AAP.[51] No effect on magnesium excretion was observed. Silybin did not interfere with the antineoplastic effects of cisplatin or ifosfamide in germ cell tumors. In experiments with ovarian and breast cancer cell lines, silybin potentiated the effect of cisplatin and doxorubicin.[13] IdB 1,016, a form of silybin bound to a phospholipid complex, was found to enhance the activity of cisplatin against A2780 ovarian cancer cells but had no effect on its own. [52] Silybin increased the chemosensitivity of DU 145 prostate cancer cells resistant to chemotherapy.[53]

Studies have also investigated the effect of silymarin on tumor initiation and promotion. Silymarin appears to have a chemopreventive effect through perturbations in the cell cycle, altering cell signaling that induces cellular proliferation, affecting angiogenesis, or through its anti-inflammatory properties.[1,7,13,19,54] These findings have been supported in human prostate, breast, ectocervical, ovarian, hepatic, leukemia, and epidermoid cell lines.[4,7,9,10,15,55] An investigation of the effect of silymarin on ultraviolet B radiation-induced nonmelanoma skin cancer in mice found that silymarin treatment significantly reduced tumor incidence ($P < .003$), tumor multiplicity ($P < .0001$), and tumor volume ($P < .0001$).[19] These findings suggest that silymarin plays a prominent role in the reduction of cancer cells and in preventing the formation of cancer cells. A number of studies have investigated the mechanism through, which silymarin may affect tumor promotion in mouse skin tumor models. Studies have found that silymarin reduces transcription of markers of tumor promotion and activity,[19] inhibits transcription of tumor promoters,[56] stimulates antioxidant activities,[19,23] interferes with cell signaling,[55] inhibits inflammatory actions,[19,22] and modulates cell-cycle regulation.[57]

In prostate cancer cell lines, silybin has been shown to inhibit growth factors and stimulate cell growth,[1-3,5] promote cell cycle arrest,[1,4] and inhibit antiapoptotic activity.[53] In rats with azoxymethane -induced colon cancer, dietary silymarin resulted in a reduction in the incidence and multiplicity of adenocarcinoma of the colon in a dose-dependent manner.[25,26] Dietary silymarin had no effect on small intestinal adenocarcinoma,[26] but exerted a preventive effect in mice with N-butyln-(4-hydroxybutyl) nitrosamine –induced bladder cancer [24] and in F344 rats with 4-nitroquinoline 1-oxide –induced cancer of the tongue.[17] Dietary silybin administered to nude mice with prostate carcinoma increased production of insulin-like growth factor-binding protein-3 in the plasma of mice and significantly inhibited tumor volume ($P < .05$).[2] Silibinin administered twice daily reduced the growth of colorectal tumor xenografts in mice for a period of 6 weeks.[58,59]

References

1. Zi X, Agarwal R: Silibinin decreases prostate-specific antigen with cell growth inhibition via G1


11. Shear NH, Malkiewicz IM, Klein D, et al.: Acetaminophen-induced toxicity to human epidermoid cell line A431 and hepatoblastoma cell line Hep G2, in vitro, is diminished by


22. Zhao J, Sharma Y, Agarwal R: Significant inhibition by the flavonoid antioxidant silymarin against 12-O-tetradecanoylphorbol 13-acetate-caused modulation of antioxidant and


33. Venkataramanan R, Ramachandran V, Komoroski BJ, et al.: Milk thistle, a herbal supplement,


46. Garrido A, Arancibia C, Campos R, et al.: Acetaminophen does not induce oxidative stress in


57. Singh RP, Agarwal R: Flavonoid antioxidant silymarin and skin cancer. Antioxid Redox Signal 4
Human/Clinical Studies

Two published case reports describe the use of milk thistle as either a treatment or an adjunctive therapy in individuals with cancer. One case report describes the use of milk thistle in a 34-year-old woman with promyelocytic leukemia.\[1\] The investigators administered 800 mg of silymarin during the patient’s maintenance therapy, which consisted of treatment with methotrexate and 6-mercaptopurine. During the 4 months of treatment with silymarin, the patient who previously required intermittent breaks in therapy due to abnormal liver enzyme levels had normal liver enzyme levels with no further interruption of therapy. A second case report describes a 52-year-old man with hepatocellular carcinoma.\[2\] The patient began taking 450 mg of silymarin per day, and spontaneous regression of the tumor was reported in the absence of initiation of anticancer therapy.

In a double-blind, placebo-controlled trial, 50 children who were undergoing treatment for acute lymphoblastic leukemia and who had chemotherapy-related hepatotoxicity were randomly assigned to receive silymarin or placebo for a 4-week period.\[3\] Four weeks following completion of the intervention, the silymarin group had a significantly lower aspartate aminotransferase (AST) ($P = .05$) and a trend towards a significantly lower alanine aminotransferase (ALT) ($P = .07$). Fewer chemotherapy dose reductions were observed in the silymarin group compared to the placebo group; however, the difference was not significant. No adverse events were reported.

Most clinical trials of milk thistle have been conducted in patients with either hepatitis or cirrhosis. Other studies have investigated milk thistle in patients with hyperlipidemia, diabetes, and Amanita phalloides mushroom poisoning. Ten randomized trials [3-12] have been reported in patients with hepatitis or cirrhosis, and one randomized trial has reported the use of silymarin as a prophylaxis to iatrogenic hepatic toxicity.\[13\] Endpoints for these trials have included serum levels of bilirubin and/or the liver enzymes AST and ALT, as higher levels are an indicator of liver inflammation, damage, or disease. The lowering of these serum levels is a sign of an improving condition. In patients with hepatitis A and B, one clinical trial found silymarin (140 mg daily for 3–4 weeks) resulting in lower levels of AST, ALT, and bilirubin by day 5, compared with a placebo.
group. In another randomized, placebo-controlled study of patients with viral hepatitis B, silymarin (210 mg daily) had no effect on course of disease or enzyme levels.[7]

A randomized, controlled trial supported by the National Institute of Diabetes and Digestive and Kidney Diseases examined patients with chronic hepatitis C who had failed prior antiviral therapy. All patients had advanced chronic liver disease consisting of histologic evidence of either marked fibrosis or cirrhosis. The Hepatitis C Antiviral Long-Term Treatment Against Cirrhosis trial used a half dose of pegylated interferon versus no treatment; the treatment was to be administered for 3.5 years.[12] The aim was to reduce progression of chronic hepatitis C, particularly in the development of hepatocellular carcinoma. Among 1,145 study participants, 56% had never taken herbals, 21% admitted past use, and 23% were using herbals at enrollment. Silymarin constituted 72% of the 60 herbals used at enrollment. Users had significantly fewer symptoms and a better quality of life than nonusers. In follow-up, silymarin use was associated with reduced progression of fibrosis to cirrhosis but without an impact on clinical outcome.[15]

Although there are many reports of the use of herbals for the treatment of chronic liver diseases, most treatment trials have suffered from poor scientific design, uncertainty of the required dosage of herbals, and an insufficient number of study participants. A recent review of complementary and alternative medications (CAM) to treat liver diseases focused on the classification, epidemiology, and the philosophy of CAM and reviewed the criteria needed to conduct a scientifically valid research study focusing on herbal products.[16]

There has been skepticism regarding the evidence that silymarin has a direct impact on the hepatitis C virus (HCV)—some studies suggest that it does, but most studies are unable to confirm these reports. However, at least two articles in major journals have suggested that silymarin or its congeners may inhibit HCV. In one report, investigators found that a standardized silymarin extract inhibited tumor necrosis factor -alpha in anti-CD3-stimulated human peripheral blood mononuclear cells and nuclear factor-kappa B-dependent transcription in human hepatoma Huh-7 cells.[17] Silymarin also displayed prophylactic and therapeutic effects against HCV infection and when combined with interferon-alpha, was more inhibitory of HCV replication than was interferon alone. This indicates that silymarin has anti-inflammatory and antiviral effects in patients with chronic hepatitis C.

In a case series /phase I study, patients with HCV were treated with intravenous silibinin with and without PEG-interferon and ribavirin.[18] In the case series, 16 HCV nonresponder patients were administered intravenous silibinin in a dose of 10 mg/kg/day for 7 days. Subjects then began treatment with oral silibinin in combination with PEG-interferon and ribavirin for 12 weeks. At the end of the study period, all patients were positive for HCV RNA, but 5 of 13 completed patients had reductions in HCV RNA. Significance was not reported. In the same study, the authors presented results of a phase I study in which 20 patients were administered 5 mg/kg, 10 mg/kg,
15 mg/kg, or 20 mg/kg of silybinin for 14 days in combination with PEG-interferon and ribavirin (initiated on day 8). A significant drop in HCV RNA was observed on day 7 in patients administered the 10 mg/kg, 15 mg/kg, and 20 mg/kg doses of silybinin. Further declines were observed in HCV RNA with administration of PEG-interferon and ribavirin. Except for mild gastroenteritis, intravenous silibinin monotherapy was well tolerated.

Patients in a phase I pharmacokinetics study for the evaluation of absorption characteristics and determination of effective doses received increasing oral doses of silymarin.[19] A subsequent multicenter, double-blind, placebo-controlled trial, involving 154 patients with chronic HCV infection who had previously failed interferon-based treatment and had raised ALT levels, was performed.[20] Patients were randomly assigned to receive 420 mg of silymarin, 700 mg of silymarin, or a matching placebo orally 3 times per day for 24 weeks, with the aim of reducing ALT levels to less than 40 U/L or less than 65 U/L if this was at least a 50% decline from the baseline level. In this study, silymarin given orally in higher-than-usual doses failed to significantly reduce serum ALT levels. No significant adverse effects were associated with silymarin. In one of the largest observational studies involving 2,637 patients with chronic liver disease, 8-week treatment with 560 mg/day of silymarin resulted in reductions of serum AST, ALT, and gamma-glutamyltranspeptidase ([GGT], a marker of bile duct disease) and a decrease in the frequency of palpable hepatomegaly.[21]

Another published report describes the use of silybinin as the only effective antidote in patients with liver damage from Amanita phalloides (Fr.) Link poisoning.[22] Patients were administered doses of 35 to 55 mg/kg body weight, with no reports of adverse events. A recent retrospective review of the treatment for Amanita phalloides poisoning suggests that silymarin continues to be a promising drug in the treatment of this mushroom poisoning.[23] The beneficial effect of silymarin on liver histology suggests it has a role in the prevention of hepatitis and/or hepatocellular carcinoma; however, no clinical trials in humans have investigated these uses of silymarin.

### Clinical Studies Investigating Silymarin in the Treatment or Prevention of Liver Disease

<table>
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<tr>
<th>Reference Citation</th>
<th>Type of Study</th>
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<th>No. of Patients: Enrolled; Treated; Controla</th>
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<th>Reference</th>
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<th>Disease</th>
<th>Study Size</th>
<th>Study Outcomes</th>
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<td>Double-blind, placebo-controlled, randomized clinical trial</td>
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<td>[9]</td>
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<td>Cirrhosis</td>
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<td>Increased survival</td>
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<td>[4]</td>
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<td>Reduction in ALT and gamma-glutamyl transpeptidase</td>
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<td>[7]</td>
<td>Controlled, randomized trial</td>
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<td>52(^d), 20-silymarin, 20-misoprostol; 12</td>
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<td>[6]</td>
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<td>Alcohol-induced cirrhosis</td>
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<td>[10]</td>
<td>Double-blind, placebo-controlled, randomized clinical trial</td>
<td>Alcohol-induced cirrhosis</td>
<td>60(^f), 24; 25</td>
<td>Significant increases in erythrocyte glutathione and decreased platelet MDA values; no significant</td>
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<td>[8]</td>
<td>Nonrandomized pilot study</td>
<td>Primary biliary cirrhosis</td>
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<td>[18]</td>
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<td>[11]</td>
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<td>60; 30; 30</td>
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<td>[12]</td>
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<td>Chronic hepatitis C</td>
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<td>[3]</td>
<td>Double-blind,</td>
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<td>50; 24; 26</td>
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Current Clinical Trials

Check NCI’s list of cancer clinical trials for cancer CAM clinical trials on milk thistle and silymarin that are actively enrolling patients.

General information about clinical trials is also available from the NCI Web site.

References

1. Invernizzi R, Bernuzzi S, Ciani D, et al.: Silymarine during maintenance therapy of acute

ALL = acute lymphoblastic leukemia; ALT = alanine aminotransferase; HCV = hepatitis C virus; LFT = liver function test; No. = number.

Number of patients treated plus number of patients controlled may not equal number of patients enrolled; number of patients enrolled = number of patients initially recruited/considered by the researchers who conducted a study; number of patients treated = number of enrolled patients who were administered the treatment being studied AND for whom results were reported; historical control subjects are not included in number of patients enrolled.

Nine patients were excluded from the final analysis (seven patients missed appointments, and two patients were missing data requirements).

Study investigated dose-response relationships. Patients were randomly assigned to receive 80 mg 2 times a day (n = 20), 120 mg 2 times a day (n = 20), or 120 mg 3 times a day (n = 20). The effective dose was 120 mg 2 times a day and 120 mg 3 times a day.

Patients were randomly assigned to the misoprostol and silymarin groups. Twelve nonrandomized patients served as controls.

Fifteen patients were lost to follow-up, 18 patients were deceased, and 42 patients withdrew from the study (adverse events, noncompliance, and voluntary withdrawal).

Eleven patients did not complete the trial (voluntary withdrawal, disease progression, and one adverse event).


Adverse Effects

Human studies of silymarin have shown minimal adverse effects in multiple large, blinded, placebo-controlled, randomized studies. Silymarin is well tolerated, with only rare reports of a mild laxative effect. Mild allergic reactions have been seen at high doses (>1,500 mg /day),

http://www.cancer.gov/about-cancer/treatment/cam/hp/milk-thistle-pdq#section/all
although the details of these allergic reactions were not reported.[1] A recent case report from Australia described a reaction to a milk thistle extract that included intermittent episodes of sweating, abdominal cramping, nausea, vomiting, diarrhea, and weakness.[2] All symptoms resolved when the silymarin was discontinued. The authors suggested that the capsules were contaminated; the type of contamination was unknown.

According to the German Commission E, there are no reported side effects with milk thistle within the recommended doses. Rare cases of milk thistle having a laxative effect have been reported. Human studies have reported stomach upset, heartburn, and transient headaches; however, none of these symptoms were attributed to supplementation with milk thistle, and supplementation was not discontinued.[3] One human dosing study reported nausea, heartburn, and dyspepsia in patients treated with 160 mg/day, dyspepsia in patients treated with 240 mg/day, and postprandial nausea and meteorism in patients treated with 360 mg/day. None of these side effects were dose related.

Silymarin has been well tolerated in high doses. Silymarin has been used in pregnant women with intrahepatic cholestasis at doses of 560 mg/day for 16 days, with no toxicity to the patient or the fetus.[4] The published data on silymarin use in children focuses on intravenous doses of 20 to 50 mg/kg body weight for mushroom poisoning.[5] Silymarin has also proved nontoxic in rats and mice when administered in doses as high as 5,000 mg/kg body weight. Rats and dogs have received silymarin at doses of 50 to 2,500 mg/kg body weight for a 12-month period. Investigations, including postmortem analyses, showed no evidence of toxicity.

It is not known whether milk thistle may reduce, enhance, or have no effect on the effectiveness of chemotherapy. Silymarin decreases the activity of the cytochrome P450 enzyme system, which is involved in the clearance of certain chemotherapy drugs.[6] However, the dose at which inhibition is observed is high and not achieved with oral intake of silymarin.[7] One study investigated the effects of silymarin on the pharmacokinetics of irinotecan. Oral administration of milk thistle (200 mg, a clinically relevant dose, 3 times per day) had no significant effects on the pharmacokinetics of irinotecan. The authors concluded that the recommended doses of milk thistle are too low to affect activity of CYP3A4 or UGT1A1 enzyme pathways.[8]

Theoretically, milk thistle may also interact adversely with chemotherapy drugs that exert their cytotoxic effects through the generation of free radicals. Silymarin and its metabolite inhibit P-glycoprotein–mediated cellular efflux, leading to the potentiation of doxorubicin cytotoxicity.[9] No trials have been performed to support or negate these theoretical considerations. No effects on indinavir and alcohol pharmacokinetics have been observed. Enhancement of antiarrhythmic effects of amiodarone in rats has been observed.[9]

References

http://www.cancer.gov/about-cancer/treatment/cam/hp/milk-thistle-pdq#section/all


**Summary of the Evidence for Milk Thistle**

To assist readers in evaluating the results of human studies of complementary and alternative medicine (CAM) treatments for cancer, the strength of the evidence (i.e., the levels of evidence) associated with each type of treatment is provided whenever possible. To qualify for a level of evidence analysis, a study must:

- Be published in a peer-reviewed scientific journal.
- Report on therapeutic outcome or outcomes, such as tumor response, improvement in survival, or measured improvement in quality of life.
- Describe clinical findings in sufficient detail for a meaningful evaluation to be made.

Separate levels of evidence scores are assigned to qualifying human studies on the basis of statistical strength of the study design and scientific strength of the treatment outcomes (i.e., endpoints) measured. The resulting two scores are then combined to produce an overall score. A
level of evidence score cannot be assigned to milk thistle because there has been insufficient clinical research to date. For an explanation of the scores and additional information about levels of evidence analysis of CAM treatments for cancer, refer to Levels of Evidence for Human Studies of Cancer Complementary and Alternative Medicine.

Given the limited amount of human data, the use of milk thistle/silymarin as a treatment for cancer patients cannot be recommended outside the context of well-designed clinical trials.

Changes to This Summary (03/26/2015)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

An editorial change was made to this summary.

This summary is written and maintained by the PDQ Cancer Complementary and Alternative Medicine Editorial Board, which is editorially independent of NCI. The summary reflects an independent review of the literature and does not represent a policy statement of NCI or NIH. More information about summary policies and the role of the PDQ Editorial Boards in maintaining the PDQ summaries can be found on the About This PDQ Summary and PDQ NCI's Comprehensive Cancer Database pages.

About This PDQ Summary

Purpose of This Summary

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the use of milk thistle in the treatment of people with cancer. It is intended as a resource to inform and assist clinicians who care for cancer patients. It does not provide formal guidelines or recommendations for making health care decisions.

Reviewers and Updates

This summary is reviewed regularly and updated as necessary by the PDQ Cancer Complementary and Alternative Medicine Editorial Board, which is editorially independent of the National Cancer Institute (NCI). The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH).
Board members review recently published articles each month to determine whether an article should:

- be discussed at a meeting,
- be cited with text, or
- replace or update an existing article that is already cited.

Changes to the summaries are made through a consensus process in which Board members evaluate the strength of the evidence in the published articles and determine how the article should be included in the summary.

The lead reviewers for Milk Thistle are:

- John A. Beutler, PhD (National Cancer Institute)
- Kara Kelly, MD (Columbia University)
- Elena J. Ladas, PhD, RD (Columbia University)

Any comments or questions about the summary content should be submitted to Cancer.gov through the Web site's Contact Form. Do not contact the individual Board Members with questions or comments about the summaries. Board members will not respond to individual inquiries.

### Levels of Evidence

Some of the reference citations in this summary are accompanied by a level-of-evidence designation. These designations are intended to help readers assess the strength of the evidence supporting the use of specific interventions or approaches. The PDQ Cancer Complementary and Alternative Medicine Editorial Board uses a formal evidence ranking system in developing its level-of-evidence designations.

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Updated: March 26, 2015

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Mistletoe Extracts—for health professionals (PDQ®)

Overview

This complementary and alternative medicine (CAM) information summary provides an overview of the use of mistletoe as a treatment for people with cancer. The summary includes a brief history of mistletoe research, the results of clinical trials, and possible side effects of mistletoe use.

This summary contains the following key information:

- Mistletoe is a semiparasitic plant that has been used for centuries to treat numerous human ailments.
- Mistletoe is used commonly in Europe, where a variety of different extracts are manufactured and marketed as injectable prescription drugs. These injectable drugs are not available commercially in the United States and are not approved as a treatment for people with cancer.
- Mistletoe is one of the most widely studied CAM therapies for cancer. In certain European countries, the preparations made from European mistletoe (Viscum album, Loranthaceae) are among the most prescribed drugs offered to cancer patients.[1]
- Although mistletoe plants and berries are considered poisonous to humans, few serious side effects have been associated with mistletoe extract use.
- The use of mistletoe as a treatment for people with cancer has been investigated in clinical studies. Reports of improved survival and/or quality of life have been common, but nearly all of the studies had major weaknesses that raise doubts about the reliability of the findings.
- At present, the use of mistletoe cannot be recommended outside the context of well-designed clinical trials. Such trials will be valuable to determine more clearly whether mistletoe can be useful in the treatment of specific subsets of cancer patients.

Many of the medical and scientific terms used in this summary are hypertext linked (at first use in each section) to the NCI Dictionary of Cancer Terms, which is oriented toward nonexperts. When a
linked term is clicked, a definition will appear in a separate window.

Reference citations in some PDQ CAM information summaries may include links to external Web sites that are operated by individuals or organizations for the purpose of marketing or advocating the use of specific treatments or products. These reference citations are included for informational purposes only. Their inclusion should not be viewed as an endorsement of the content of the Web sites, or of any treatment or product, by the PDQ Cancer CAM Editorial Board or the National Cancer Institute.

References


General Information

Mistletoe, a semiparasitic plant, holds interest as a potential anticancer agent because extracts derived from it have been shown to kill cancer cells \textit{in vitro} \cite{1-10} and to stimulate immune system cells both \textit{in vitro} and \textit{in vivo} \cite{10-24}. Two components of mistletoe, namely viscotoxins, polysaccharides and lectins, may be responsible for these effects.\cite{10-13,17-19,21-23,25-32} Viscotoxins are small proteins that exhibit cell-killing activity and possible immune-system-stimulating activity.\cite{1,6,18,19,33,34} Lectins are complex molecules made of both protein and carbohydrates that are capable of binding to the outside of cells (e.g., immune system cells) and inducing biochemical changes in them.\cite{10,35-38} In view of mistletoe’s ability to stimulate the immune system, it has been classified as a type of biological response modifier.\cite{35} Biological response modifiers constitute a diverse group of biological molecules that have been used individually, or in combination with other agents, to treat cancer or to lessen the side effects of anticancer drugs. Mistletoe extracts have been demonstrated in preclinical settings to have other mechanisms of action, such as antiangiogenesis.\cite{39}

Preparations from mistletoe extracts are most frequently used in the treatment of cancer patients in German-speaking countries.\cite{40} Commercially available extracts are marketed under a variety of brand names, including Iscador (see explanation of suffixes below), Eurixor, Helixor, Isorel, Iscucin, Plenosol, and abnobaVISCUM. Some extracts are marketed under more than one name. Iscador, Isorel, and Plenosol are also sold as Iscar, Vysorel, and Lektinol, respectively. All of these products are prepared from \textit{Viscum album} (Loranthaceae) (\textit{Viscum album} L. or European mistletoe). They are not sold as a drug in the United States. Eurixor, Isorel, and Vysorel are no longer available on the market for sale.

In addition to European mistletoe, extracts from a type of Korean mistletoe (\textit{Viscum album} var.
coloratum [Kom.] Ohwi) have demonstrated in vitro and in vivo cytotoxicity in laboratory studies. [41-45]

Mistletoe grows on several types of trees, and the chemical composition of extracts derived from it depends on the species of the host tree (e.g., apple, elm, oak, pine, poplar, and spruce), the time of year harvested, how the extracts are prepared, and the commercial producer. [8,36,46-49]

Mistletoe extracts are prepared as aqueous solutions or solutions of water and alcohol, and they can be fermented or unfermented. [4,6,20,46,47,50-53] Some extracts are prepared according to homeopathic principles, and others are not. Accordingly, as homeopathic preparations, they are typically not chemically standardized extracts. [10,54] In addition, the commercial products can be subdivided according to the species of host tree, which is typically indicated in the product name by a suffix letter. Iscador, a fermented aqueous extract of Viscum album L. that is prepared as a homeopathic drug, is marketed as IscadorM (from apple trees; Malus domestica), IscadorP (from pine trees; Pinus sylvestris), IscadorQu (from oak trees; Quercus robur), and IscadorU (from elm trees; Ulmus minor). Helixor, an unfermented aqueous extract of Viscum album L. that is standardized by its biological effect on human leukemia cells in vitro, is marketed as HelixorA (from spruce trees; Picea abies), HelixorM (from apple trees), and HelixorP (from pine trees; Pinus sylvestris). [51] Eurixor (which is no longer available on the market for sale), an unfermented aqueous extract of Viscum album L. harvested from poplar trees, is reportedly standardized to contain a specific amount of one of mistletoe’s lectins (i.e., the lectin ML-1; refer to the History section of this summary for more information). [51] Some proponents contend the choice of extract should depend on the type of tumor and the gender of the patient. [49,51,55,56]

A recombinant ML-1 from Escherichia coli bacteria known as rViscum or aviscumine has been studied in the laboratory and in phase I clinical trials. Since this is not an extract of mistletoe, it is out of the purview of this summary. [57]

Mistletoe extracts are usually given by subcutaneous injection, although administration by other routes (i.e., oral, intrapleural, intratumoral, and intravenous) has been described. [17,20-24,32,36,49,51,54,58-63] In most reported studies, subcutaneous injections were given 2 to 3 times a week, but the overall duration of treatment varied considerably.

Viscum album is listed in the Homeopathic Pharmacopoeia of the United States, which is the officially recognized compendium for homeopathic drugs in this country. [64] Although the U.S. Food and Drug Administration (FDA) has regulatory authority over homeopathic drugs, this authority is usually not exercised unless the drugs are formulated for injection or there is evidence of severe toxicity. At present, the FDA does not allow the importation or distribution of injectable preparations of mistletoe, including homeopathic formulations, except for the purpose of clinical research. The extracts are not available commercially in the United States and are not
approved as a treatment for people with cancer.

Before researchers can conduct clinical drug research in the United States, they must file an Investigational New Drug (IND) application with the FDA. IND approval is also required for clinical investigation of homeopathic drugs. The FDA does not disclose information about IND applications or approvals; this information can be released only by the applicants. At least two U.S. investigators were given IND approval to study mistletoe as a treatment for people with cancer (NCCAM-02-AT-260 and TJUH-01F.45).

In this summary, the mistletoe extract or product used in each study will be specified wherever possible.

References


http://www.cancer.gov/about-cancer/treatment/cam/hp/mistletoe-pdq#section/all


History

Mistletoe has been used for centuries for its medicinal properties.[1-6] It was reportedly used by the Druids and the ancient Greeks, and it appears in legend and folklore as a panacea. It has been used in various forms to treat cancer, epilepsy, infertility, menopausal symptoms, nervous tension, asthma, hypertension, headache, and dermatitis. Modern interest in mistletoe as an anticancer treatment began in the 1920s. Most of the results of clinical studies have been published exclusively in German. Refer to the Human/Clinical Studies section of this summary for more information.

Another reported activity that may be relevant to optimum functioning of the immune system in individuals with cancer is stabilization of the DNA in white blood cells, including white blood cells...
that have been exposed to DNA-damaging chemotherapy drugs.[7-11]

Mistletoe has been shown to stimulate increases in the number and the activity of various types of white blood cells.[2,3,9,11-53] Immune-system-enhancing cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor -alpha, are released by white blood cells after exposure to mistletoe extracts.[1,3,7,9-11,14,19,29,33,37,42-46,48-50,52-54] Other evidence suggests that mistletoe exerts its cytotoxic effects by interfering with protein synthesis in target cells [3,4,8,11,33,42-46,52,55-63] and by inducing apoptosis.[3,11,36,42,46,52,64-66] Mistletoe may also serve a bridging function, bringing together immune system effector cells and tumor cells.[18,67]

References


http://www.cancer.gov/about-cancer/treatment/cam/hp/mistletoe-pdq#section/all


Laboratory/Animal/Preclinical Studies

The immune-system-stimulating and cytotoxic properties of mistletoe have been investigated in laboratory and animal studies.

Viscotoxins and lectins have been investigated as active components in mistletoe; most research has focused on the lectins.[1-9] Purified mistletoe lectins have demonstrated cytotoxic and immune-system-stimulating activities. To date, four different lectins: ML-1, ML-2, ML-3, and Viscum album chitin-binding agglutinin have been identified in mistletoe extracts. ML-1 (or viscum) may be responsible for many of mistletoe’s biological effects. When a laboratory method was used to selectively deplete ML-1 from Viscum album extracts, their cytotoxic and immune-system-stimulating properties were markedly reduced.[10,11] It should be noted that fermentation eliminates most of the ML-1 in mistletoe extracts.[12-14] Polysaccharide and oligosaccharide components of mistletoe extracts with substantial immune-stimulating properties have been reviewed.[15,16]

The molecular structure of ML-1 consists of an alpha chain and a beta chain, which can be separated from one another.[1,1,6-9,13,17,18] Each chain type appears to mediate a subset of the activities described for the intact lectin. Cytotoxicity is associated mainly with the alpha chain. In laboratory studies, the ML-1 alpha chain has been coupled to monoclonal antibodies to produce immunotoxins that target and kill specific cell types.[19-21]

Recombinant ML-1, rML (also known as rViscunim or aviscumin) appears to have the same efficacy as plant-based ML-1 in laboratory studies.[22] Since this is not an extract of mistletoe, it is out of the purview of this summary.

The beta chain of ML-1 is responsible for binding to the surface of a target cell.[23] Studies of mistletoe lectin binding to cancer cells have examined whether the extent of cell binding can predict disease outcome or survival. Studies show that the prognostic value of ML-1 binding depends on the type of cancer.[24] For human breast cancer cells, the amount of lectin-bound cells correlates positively with disease outcome. However, for human adenocarcinoma of the lung, there is no correlation between the amount of lectin-bound cells and disease survival.[25] Though much research has looked at this particular aspect, there have not been studies that directly link the concentration of that component to any clinical activity of mistletoe.

Laboratory studies have shown that mistletoe extracts can stimulate the activity of white blood cells in vitro and cause them to release molecules thought to be important for anticancer immune responses. [4,6,8,9,17,26-33] In addition, mistletoe extracts have demonstrated cytotoxic activity against a variety of mouse, rat, and human cancer cells in vitro.[1,8,23,34-37]

There are conflicting reports concerning the stimulation of cancer cell growth in vitro. In one
study, the \textit{in vitro} growth of several types of human cancer cells was stimulated by treatment with low doses of the purified lectin ML-1.\cite{1}\) However, various other studies found that ML-1 and mistletoe extracts did not induce cell proliferation.\cite{38,39}

A 2004 \textit{in vitro} study of IscadorQu, a fermented aqueous extract from European mistletoe grown on oaks, against various cell lines demonstrated that sensitivity to this extract varies greatly among cell lines. In sensitive cell lines, a strong effect was seen in epidermal (HaCaT), lung adenocarcinoma (NCI-H125), and breast adenocarcinoma (MCF-7) cell lines whereas, little or no effect was seen in lung squamous cell carcinoma (MR65) and colon carcinoma (Cac0-2, HT-29). Some cell lines were responsive to high or low concentrations of IscadorQu. IscadorQu showed early cell cycle inhibition followed by apoptosis in a dose-dependent manner.\cite{40}

Studies of the ability of mistletoe to inhibit cancer cell growth in animals have yielded mixed and inconsistent results.\cite{5-9,36,41-49}\) In most of these studies, mistletoe extracts were administered either by subcutaneous injection or by intraperitoneal injection.

In one animal study, treatment with IscadorM increased the survival time of mice that had been implanted with Ehrlich ascites mouse cancer cells, but not L1210 leukemia or B16 melanoma cancer cells.\cite{50}\) The effect of IscadorM on the growth of tumors formed in mice by three additional types of mouse cancer cells (i.e., Lewis lung carcinoma, colon adenocarcinoma 38, and C3H mammary adenocarcinoma) was also assessed in this study. Treatment with IscadorM substantially reduced the growth rate of all three types of tumors.

In another animal study, mice were administered IscadorM before, during, or after injection with either of two types of mouse cancer cells (i.e., Dalton lymphoma or Ehrlich ascites).\cite{51}\) In this study, all groups of mice treated with mistletoe showed substantially slower tumor growth than the control groups.

No antitumor effect or improvement in survival was observed when IscadorM was used to treat rats bearing chemically induced mammary carcinomas or tumors formed from rat Walker 256 carcinosarcoma cells.\cite{52}\) In this study, IscadorM was also not effective in treating mice that had been injected with Ehrlich ascites cells. In addition, IscadorP was found ineffective in treating rats with tumors formed from rat L5222 leukemia cells.

In another study, intratumoral injections of mistletoe extract (abnobaVISCUM Fraxini-2) demonstrated more antitumor activity than intravenous gemcitabine when injected into mouse xenografts of human pancreatic cancer.\cite{53}

Treatment with the mistletoe extract Lektinol (also sold as Plenosol; refer to the General Information section of this summary for more information) has likewise yielded mixed results in animal experiments.\cite{7}\) Treatment with Lektinol slowed the growth of tumors formed in mice from implants of three types of mouse cancer (i.e., colon adenocarcinoma 38, Renca renal cell
carcinoma, and F9 testicular carcinoma) but not in two other mouse cancers (i.e., B16 melanoma and Lewis lung carcinoma).

The anticancer effects of Isorel (also sold as Vysorel; refer to the General Information section of this summary for more information) have been examined in at least two animal studies.[36,54] In one study, IsorelM was used alone or in combination with local x-ray therapy in mice bearing mouse CMC-2 fibrosarcoma tumors.[54] When IsorelM was used alone, no effect on either tumor growth or animal survival was observed. When IsorelM injections were combined with local x-ray therapy of tumors, substantial improvements in survival were found in comparison with the survival of mice treated with local x-ray therapy alone. With local x-ray therapy alone, 22% of mice were cured of their tumors. When local x-ray therapy was combined with IsorelM injections, administered before or after the x-ray treatment, the cure rate increased to 43%. When IsorelM was administered both before and after local x-ray therapy, the proportion of cured mice increased to 67%.

In another study, IsorelM showed antitumor and antimetastatic effects in mice that had been injected with mouse mammary carcinoma cells.[36] The antitumor effects appeared most pronounced when IsorelM was injected in the vicinity of tumors.

The ability of purified or recombinant lectin ML-1 to inhibit the formation of chemically induced bladder tumors in rats has been evaluated in three studies.[5,8,48,55] In two of the studies, purified ML-1 was administered by subcutaneous injection.[5,8,55] Treatment with ML-1 did not reduce the frequency of bladder tumor formation or increase immune system activity in the bladder wall in either study. In the third study, recombinant ML-1 was introduced directly into the bladder through a process known as intravesical instillation.[8,48] In this study, the frequency of bladder tumor formation was reduced by approximately 50% in ML-1-treated animals. As in the other two studies, immune system activity in the bladder wall was not increased substantially. It was concluded that the antitumor effect observed in this study was the result of direct cytotoxic action by the recombinant lectin against malignant cells.[48]

A few animal studies have suggested that mistletoe is beneficial in decreasing the side effects of conventional anticancer therapy (e.g., chemotherapy and radiation therapy) and that it counteracts the effects of drugs used to suppress the immune system.[56-59] In one study, IscadorM was shown to increase the number of white blood cells in mice treated with cyclophosphamide chemotherapy or radiation therapy and to decrease the amount of weight loss due to radiation, but not during cyclophosphamide treatment.[58] In another study, IscadorM was shown to accelerate the recovery of hematopoietic tissue in the bone marrow and spleens of irradiated rats and mice.[56] In another study, the mistletoe product Eurixor was shown to counteract the immunosuppressive effects of treatment with the drug cortisone.[57] In this in vitro study, mistletoe (Viscum album L.) did not inhibit chemotherapy-induced cytostasis or
cytotoxicity. [60]

References


35. Maier G, Fiebig HH: Absence of tumor growth stimulation in a panel of 16 human tumor cell


2002. [PUBMED Abstract]


Human/Clinical Studies

Mistletoe has been evaluated as a treatment for people with cancer in numerous clinical studies. [1-20]

The mistletoe extracts and products studied in clinical trials were Iscador, Eurixor, Helixor, Lektinol, Isorel, abnobaVISCUM,[21] and recombinant lectin ML-1 (refer to the appropriate sections and tables at the end of this section for more information).

The findings from more than 50 clinical trials of mistletoe extracts in patients with cancer have been published, and several systematic reviews and meta-analyses of the results of these studies have been performed. Three of the most recent systematic reviews addressed quality of life (QOL), survival, and symptom relief in patients with various cancer types.[18,20,22] Most studies reported an improvement in QOL.

In one systematic review that examined 26 randomized controlled trials (RCTs), 22 trials reported an improvement in QOL. All 10 of the nonrandomized controlled trials also reported the same benefit. Improvement in fatigue, nausea and vomiting, depression, emotional well-being, and concentration were reported. Some of the studies were well designed, while others reported weaknesses.[22]

Tumor response, QOL, and psychological distress were measured in a review of 21 RCTs of various cancers in which different mistletoe preparations were used either alone, with chemotherapy, or with radiation therapy.[18] Survival times were included in 13 of the studies. Most of the studies reported benefits for patients, although this review was limited by small sample size and methodological weaknesses. Thus, the authors were unable to suggest practice guidelines for the use of mistletoe.

The oldest of these three reviews investigated the results of 10 RCTs that used a variety of mistletoe extracts in patients with various malignancies. There was no difference in survival or other benefits for cancer patients who received mistletoe. Therefore, mistletoe was not recommended as a curative or supportive care therapy.[20]

A systematic review of all controlled clinical studies of mistletoe found consistent improvement in chemotherapy-associated fatigue as well as other QOL measures.[22]

Although mistletoe was found to be therapeutically effective in most of the reported studies, many of the studies had one or more major design weaknesses as mentioned above that raised doubts about the reliability of the findings. These weaknesses include registration of small
numbers of patients; presence of large numbers of patients who either were not evaluable or were otherwise excluded from the analyses; failure to adequately document mistletoe use, mistletoe dose, and/or interruptions of mistletoe use; absence of control subjects or use of historical control subjects; use of inadequate randomization procedures; absence of treatment blinding; extensive use of subset analysis; and the measurement of mean as opposed to median survival. (Note: In studies with small numbers of patients, the mean survival time can be greatly exaggerated if one or more patients exhibit unusually long survival; median survival, therefore, is a less biased measure.) In addition, evaluation of the studies is often hindered by incomplete descriptions of the study design and by incomplete reporting of clinical data, including data about previous and concurrent therapies received by the patients. A selection of studies is discussed below, organized by the type of mistletoe extract used. Eurixor, Isorel, and Vysorel are no longer available on the market for sale.

### Iscador

An interim analysis of a randomized phase III trial reported on 220 patients with locally advanced or metastatic pancreatic cancer.[23] Patients received best supportive care and were randomly assigned to receive either IscadorQu or no antineoplastic therapy (control). Patients were stratified according to tumor stage, age, and performance status. Iscador was administered subcutaneously in a dose-escalating manner from 0.01 mg to 10 mg three times per week. Treatment with Iscador demonstrated a significant enhancement of overall survival (OS) (4.8 months vs. 2.7 months for IscadorQu patients vs. control patients, respectively; prognosis-adjusted hazard ratio [HR], 0.49; \( P < .0001 \)). Patients were further stratified into two groups based on their expected prognostic factors:

- **Poor prognosis**—patients who met at least two of the three following criteria:
  1. Union for International Cancer Control class of stage IV.
  2. Older than 65 years.
  3. Eastern Cooperative Oncology Group score greater than 2.
- **Good prognosis**—all other patients.

Subgroup analysis demonstrated clinically relevant enhancement in the survival of both groups of patients who received Iscador. The median OS in patients who were classified as having a good prognosis was 6.6 months for the Iscador group versus 3.2 months for controls (HR, 0.43; \( P < .0001 \)). Patients classified with a poor prognosis had a median OS of 3.4 months for the Iscador group versus 2.0 months for controls (HR, 0.55; \( P = .0031 \)). For patients who received Iscador, the frequency and severity of post baseline disease-related symptoms were also significantly lower.
for the following:

- Pain.
- Weight loss.
- Fatigue.
- Nausea/emesis ($P < .0001$ for all parameters).
- Diarrhea ($P = .0033$).
- Anxiety ($P = .046$).

The independent data monitoring committee that reviewed the interim analysis results recommended termination of the trial because of statistically significant superiority of survival in the treatment group, compared with the control group.

A three-arm, randomized phase III trial that involved 408 patients with previously untreated, inoperable non-small cell lung cancer was conducted between 1978 and 1987.[24] Patients were randomly assigned to one of the following treatments:

- Subcutaneous injection 3 times a week with IscadorU or IscadorQu (refer to the General Information section of this summary for more information); the concentration of mistletoe was increased during a seven-injection sequence or cycle, followed by a 3-day pause, and then the process was repeated; IscadorU was administered for two cycles, followed by two cycles of IscadorQu; both mistletoe preparations contained mercury).
- Intramuscular injection once a week with Polyerga Neu, which is a sheep spleen glycopeptide that is reported to be an immunostimulant and an inhibitor of tumor cell glycolysis.
- Intramuscular injection once a week with a vitamin B mixture, which served as a placebo.

Complete follow-up information was available for 337 patients, and 312 patients (105 Iscador treated, 100 Polyerga Neu treated, and 107 placebo treated) were included in the survival analysis. No statistically significant differences in survival were found between the three groups. Median survival for the Iscador group was 9.1 months; for the Polyerga Neu group, it was 9.0 months; and for the placebo group, it was 7.6 months. The researchers reported that 11.5% of the patients in the Iscador group survived 2 years from the time they entered the trial; the corresponding survival values for the Polyerga Neu and the placebo groups were 13.9% and 10.1%, respectively. In addition, no differences were found between the three groups with respect to tumor response, median body weight, blood chemistry values, Karnofsky Performance Status, and quality of life. However, more patients in the Iscador group than in the Polyerga Neu or the placebo groups reported subjective improvement in feelings of well-being (59.4% vs. 43.2% and 44.8%,
Another randomized phase III trial of mistletoe as a treatment for people with cancer involved 830 patients with high-risk melanoma (i.e., a primary tumor >3 mm in diameter and no regional lymph nodes positive for cancer or a primary tumor of any size, one or two regional lymph nodes positive for cancer, and no distant metastases) who were randomly assigned to one of the following four groups after potentially curative surgery: (1) treatment with low-dose interferon-alpha, (2) treatment with low-dose interferon-gamma, (3) treatment with IscadorM, or (4) no further treatment. Both types of interferon and IscadorM were administered by subcutaneous injection for a period of 1 year. The interferon injections were administered every other day, whereas IscadorM was administered 3 times a week for up to 1 year. After 8 years of follow-up, no increase in survival time or increase in time until melanoma recurrence was demonstrated for mistletoe treatment or treatment with either type of interferon.

In another retrospective multicenter cohort study that determined the safety and efficacy of Iscador as an adjuvant long-term treatment after surgery for malignant melanoma, 686 patient records were examined (357 untreated controls and 329 treated with Iscador). Safety, efficacy, and a cluster of survival endpoints (tumor related, disease free, brain metastases free, and OS) were measured. The use of additional adjuvant chemotherapy was more frequent in the Iscador-treated group, while the use of immunotherapy was more frequent in the control group. Only mild to intermediate adverse drug reactions were seen in the treated group. The tumor-related mortality rate was 8.9% in the Iscador group, compared with 10.7% in the control group (P = .017).

Three other studies of mistletoe were described in a single published report. One of the three studies was a large cohort study on the effectiveness of Iscador as a treatment for people with rectal cancer, colon cancer, breast cancer, stomach cancer, or lung cancer. The second and third studies were small, prospective, randomized, matched-pair studies (one randomized, one nonrandomized) that involved patients who were selected from a group of 8,475 individuals who had not been treated with mistletoe.

These studies are summarized in Table 1. The overall conclusion of the authors in the report of these three studies was that Iscador treatment can produce a clinically significant increase in survival in cancer patients. However, there were several weaknesses in the design and execution of these studies. In a large cohort study, the investigators were unable to find matched cohorts for 61% of eligible patients, and even among the patients for whom matches were found, fewer than two-thirds were judged to adhere strictly to the matching criteria; thus, the final analysis contained fewer than 25% of eligible patients. In the two small prospective studies, no records of the amount or duration of Iscador use were kept.
The use of Iscador as an adjuvant treatment has been examined in several studies. In the following studies, Iscador proved safe and effective and also showed a significant survival advantage over untreated controls.

A retrospective multicenter cohort study of parallel groups examined Iscador as a postoperative adjuvant using safety and efficacy as the main endpoints. A total of 1,442 patient records (710 treated patients and 732 untreated controls) were randomly selected from medical institutions that provided both standard and alternative treatments. Safety and efficacy were measured by the number and severity of adverse drug reactions. The treatment group showed significantly less adverse reactions (confidence interval = 95%; \( P = <.001 \)) compared with the controls.[26,27]

A multicenter, controlled, retrospective observational cohort study that involved nonmetastatic colorectal cancer patients treated between 1993 and 2002 was conducted to evaluate safety and efficacy measures with Iscador. Eight hundred and four consecutive colorectal patients (429 treated with Iscador and 375 controls) from 26 hospitals and practices were included. Iscador was well tolerated, with a significant reduction in adverse events, a higher rate of symptom relief, and improved disease-free survival compared with the control group. The study concluded the use of Iscador has a beneficial effect as an adjuvant therapy and long-term treatment for patients with stage I to III colorectal cancer.[28]

A randomized phase II study of Iscador combined with carboplatin-containing regimens was conducted in chemotherapy-naïve patients with advanced non-small cell lung cancer.[29] Seventy-two patients were randomly assigned to receive either chemotherapy alone with carboplatin combined with gemcitabine or pemetrexed (39 patients) or chemotherapy plus Iscador (33 patients) 3 times a week until tumor progression. Time to progression (4.8 months vs. 6 months) and OS (11 months) were similar in both treatment groups. There were no differences in QOL observed between the treatment groups, although chemotherapy dose reductions, nonhematologic toxicities, and hospitalizations were less frequent in patients treated with Iscador in this nonblinded study.

Another U.S. trial (NCT00283478) of the mistletoe extract Iscar with gemcitabine versus gemcitabine alone as a second-line therapy for non-small cell lung cancer patients who have failed one prior line of chemotherapy has been completed but not yet published.

**Table 1. Use of Iscador in Cancer Treatment: Clinical Reports Describing Therapeutic Endpoints**

<table>
<thead>
<tr>
<th>Reference Citation(s)</th>
<th>Type of Study</th>
<th>Type(s) of Cancer</th>
</tr>
</thead>
</table>

http://www.cancer.gov/about-cancer/treatment/cam/hp/mistletoe-pdq#section/all
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Cancer Type and Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>[24]</td>
<td>Randomized trial</td>
<td>Lung, non-small cell, inoperable</td>
</tr>
<tr>
<td>[30]</td>
<td>Randomized trial</td>
<td>Lung, non-small cell, stages I–IV</td>
</tr>
<tr>
<td>[5]</td>
<td>Randomized trial</td>
<td>Melanoma, stages II–III</td>
</tr>
<tr>
<td>[23]</td>
<td>Randomized trial</td>
<td>Pancreatic, advanced or metastatic</td>
</tr>
<tr>
<td>[26]</td>
<td>Comparative, retrolective, cohort study</td>
<td>Breast, stages I–IV</td>
</tr>
<tr>
<td>[25]</td>
<td>Comparative, retrolective, cohort study</td>
<td>Melanoma, stages II–III</td>
</tr>
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<td>[4]</td>
<td>Cohort study</td>
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</tr>
<tr>
<td>[28]</td>
<td>Retrospective, observational cohort study</td>
<td>Nonmetastatic colorectal</td>
</tr>
<tr>
<td>[31]</td>
<td>Nonconsecutive case series</td>
<td>Pancreatic</td>
</tr>
<tr>
<td>[32]</td>
<td>Case report</td>
<td>Lung, small cell, stage IV</td>
</tr>
</tbody>
</table>
Other Mistletoe Preparations

Eurixor

Five randomized controlled trials of Eurixor have been published as peer-reviewed articles. The largest of these studies involved 477 patients with squamous cell carcinoma of the head and neck. [2,15] These patients were randomly assigned to treatment with surgery or surgery and radiation therapy, and they were randomly assigned again to either no additional treatment or treatment with Eurixor. This double randomization produced the following four groups: (1) 105 patients treated with surgery alone; (2) 97 patients treated with surgery and Eurixor; (3) 137 patients treated with surgery and radiation therapy; and (4) 138 patients treated with surgery, radiation therapy, and Eurixor. Eurixor was administered in four treatment cycles over a 60-week period. Each treatment cycle lasted 12 weeks and was followed by a 4-week break period. During each cycle, Eurixor was administered by subcutaneous injection twice a week. Each injection contained enough standardized mistletoe extract to yield a dose of 1 nanogram of ML-1 lectin per kilogram of body weight. The results of this randomized trial showed that treatment with Eurixor did not
improve either 5-year disease-free survival or 5-year disease-specific survival. In addition, no stimulation of the immune system or improvement in quality of life was found with Eurixor treatment.

It has been suggested that a less-than-optimum dose of mistletoe was administered to patients in this trial.[4] The same dose of Eurixor, however, has been used in other clinical studies, including studies in which benefit was reported.[1,33] In addition, both the dose and the duration of Eurixor treatment in this trial are consistent with those recommended by the manufacturer.[2]

A prospective, randomized phase II trial involved 45 patients who had noninvasive bladder cancer.[3] After surgery, the patients were randomly assigned to receive either three cycles of treatment with Eurixor or no further therapy. The goal of the study was to determine whether Eurixor treatment could reduce bladder cancer recurrence. Twenty-three patients were randomly assigned to the treatment group, and 22 were randomly assigned to the control group. Each cycle of Eurixor treatment consisted of 3 months of subcutaneous injections, administered twice a week, followed by a 3-month break period. One milliliter of Eurixor was administered at each injection. After 18 months of follow-up, 11 recurrences were observed in the treatment group, and 8 were observed in the control group. The average time of recurrence for the treatment group was 6.3 months; for the control group, it was 6.4 months. The median disease-free interval for the treatment group was 9 months; for the control group, it was 10.5 months. None of these differences was considered significant.

A major concern about this study, however, is that the dose of lectin ML-1 administered to patients was not adjusted for body weight.

Eurixor is no longer available on the market for sale.

**Isorel**

Only two trials of Isorel have been reported in the publicly available, online indexed peer-reviewed medical literature. In one study, 64 patients with advanced colorectal cancer (Dukes C and D) were randomly assigned to three groups: (1) surgery and chemotherapy; (2) surgery and chemotherapy plus Isorel; and (3) surgery alone. Patients receiving treatment with Isorel had a significantly better median survival advantage and a better cumulative survival advantage than patients in the other two groups. In addition there were no side effects to treatment in the Isorel group.[34]

Another study showed that perioperative use of Isorel in patients with cancer of the digestive tract resulted in an increase in lymphocytes through 14 days of drug administration.

Isorel is no longer available on the market for sale.
Helixor

In a three-arm randomized trial, breast cancer patients were randomly assigned to one of the following groups after surgery: Helixor, chemotherapy, or control. Some patients in each group were also treated with local radiation therapy. The number of evaluable patients in the chemotherapy group was 177, with survival in the chemotherapy group superior to that in the control group and equivalent to that in the Helixor group.[35] In another three-arm randomized trial, metastatic colorectal cancer patients were randomly assigned to receive chemotherapy only (n = 20), chemotherapy plus Helixor (n = 20), or chemotherapy plus Ney-Tumorin (n = 20). Ney-Tumorin is a mixture of peptides and proteins from 15 different organs of fetal and young pigs or cows that is reported to have both antitumor and immunostimulatory properties. The mean survival time (in months) of patients treated with either Helixor or Ney-Tumorin was approximately twice that of patients treated with chemotherapy only.[36] The use of Helixor has also been examined in other studies.[37-40]

Most studies have been conducted in Europe, primarily in Germany and Austria. However, the National Center for Complementary and Integrative Health in cooperation with the National Cancer Institute (NCI) conducted a phase I trial (NCCAM-02-AT-260) of mistletoe (Helixor A) and gemcitabine in patients with advanced solid tumors. The Helixor A and gemcitabine combination showed limited toxicity, and no botanical-drug interactions were reported.[41]

abnobaVISCUM

No tumor response was seen in any of the 25 patients in a phase II trial that examined the effect of a mistletoe extract, known as abnobaVISCUM, in metastatic colorectal cancer resistant to standard treatment (5-fluorouracil and leucovorin chemotherapy). The endpoint of the study was objective tumor response. Patients were administered a gradually increasing daily dose of 0.15 mg to 15 mg. Treatment duration ranged from 4 weeks to 66 weeks. Toxicity levels were mild. Some patients reported relief of disease symptoms.[42] A small, randomized, nonblinded trial of abnobaVISCUM, given postoperatively to 15 patients with resected stage IB or II gastric cancer, showed improved quality of life among patients who received the mistletoe extract compared with 16 untreated controls.[43]

Table 2. Use of Other Mistletoe Products in Cancer Treatment: Clinical Reports Describing Therapeutic Endpoints

<table>
<thead>
<tr>
<th>Reference Citation(s)</th>
<th>Type of Study</th>
<th>Product Tested</th>
</tr>
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</table>

http://www.cancer.gov/about-cancer/treatment/cam/hp/mistletoe-pdq#section/all
<table>
<thead>
<tr>
<th></th>
<th>Reference</th>
<th>Study Type</th>
<th>Extract/Preparation</th>
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<tr>
<td>[3]</td>
<td>Randomized trial</td>
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</tr>
<tr>
<td>[1,33]</td>
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<td>Eurixor</td>
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<td>[44,45]</td>
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<td>Eurixor</td>
<td></td>
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<tr>
<td>[2]</td>
<td>Randomized trial</td>
<td>Eurixor</td>
<td></td>
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<tr>
<td>[35]</td>
<td>Randomized trial</td>
<td>Helixor</td>
<td></td>
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<tr>
<td>[36]</td>
<td>Randomized trial</td>
<td>Helixor</td>
<td></td>
</tr>
<tr>
<td>[13]</td>
<td>Randomized controlled trial</td>
<td>PS76A (Lektin)</td>
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<tr>
<td>[34]</td>
<td>Randomized trial</td>
<td>Isorel</td>
<td></td>
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<tr>
<td>[46]</td>
<td>Nonrandomized controlled trial</td>
<td>Isorel</td>
<td></td>
</tr>
<tr>
<td>[42]</td>
<td>Nonrandomized controlled trial</td>
<td>abnobaVISCUM <em>Quercus</em></td>
<td></td>
</tr>
</tbody>
</table>
Current Clinical Trials

Check NCI’s list of cancer clinical trials for cancer CAM clinical trials on mistletoe extract that are actively enrolling patients.

General information about clinical trials is also available from the NCI Web site.

References


13. Wetzel D, Schäfer M: Results of a randomised placebo-controlled multicentre study with PS76A2 (standardised mistletoe preparation) in patients with breast cancer receiving


25. Augustin M, Bock PR, Hanisch J, et al.: Safety and efficacy of the long-term adjuvant treatment of primary intermediate- to high-risk malignant melanoma (UICC/AJCC stage II and III) with a


Adverse Effects

Although a number of different mistletoe extracts have been used in human studies, the reported side effects have generally been minimal and not life threatening. Common side effects include soreness and inflammation at injection sites, headache, fever, and chills.[1-3]

One meta-analysis using *Viscum album* L. and isolated mistletoe lectins included both animal and human studies. Doses and application forms varied. No immunosuppressive effects were reported. Side effects included local reactions at the injection site and flu-like symptoms such as fever, chills, fatigue, mild gastrointestinal symptoms, and headache. High doses of mistletoe lectins resulted in reversible hepatotoxicity in some cases.[4] Another review reported adverse reactions that included local reactions at the injection site, fever, increased intracerebral pressure, headache, circulatory problems, thrombophlebitis, swelling of lymph nodes, and allergic reactions.[5]

A few cases of severe allergic reactions, including anaphylactic shock, have been reported.[2]

References


Summary of the Evidence for Mistletoe Extracts
Mistletoe is one of the most widely studied complementary and alternative medicine therapies for cancer. In certain European countries, the preparations made from European mistletoe (Viscum album L.) are among the most prescribed drugs offered to cancer patients. Mistletoe extracts have been evaluated in numerous clinical studies and improvements in survival, quality of life, and/or stimulation of the immune system have been frequently reported. However, most clinical studies conducted to date have had one or more major weaknesses that raise doubts about the reliability of the findings. In addition, no evidence exists to support the notion that stimulation of the immune system by mistletoe leads to an improved ability to fight cancer. Because all patients in the reported clinical studies appear to have been adults, no information is available about the use of mistletoe as a treatment for children with cancer.

Separate levels of evidence scores are assigned to qualifying human studies on the basis of statistical strength of the study design and scientific strength of the treatment outcomes (i.e., endpoints) measured. The resulting two scores are then combined to produce an overall score. For additional information about levels of evidence analysis, refer to Levels of Evidence for Human Studies of Cancer Complementary and Alternative Medicine.

Changes to This Summary (03/24/2015)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

Editorial changes were made to this summary.

This summary is written and maintained by the PDQ Cancer Complementary and Alternative Medicine Editorial Board, which is editorially independent of NCI. The summary reflects an independent review of the literature and does not represent a policy statement of NCI or NIH. More information about summary policies and the role of the PDQ Editorial Boards in maintaining the PDQ summaries can be found on the About This PDQ Summary and PDQ NCI's Comprehensive Cancer Database pages.

About This PDQ Summary

Purpose of This Summary

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the use of mistletoe extracts in the treatment of people with cancer. It is intended as a resource to inform and assist clinicians who care for cancer
patients. It does not provide formal guidelines or recommendations for making health care decisions.

**Reviewers and Updates**

This summary is reviewed regularly and updated as necessary by the PDQ Cancer Complementary and Alternative Medicine Editorial Board, which is editorially independent of the National Cancer Institute (NCI). The summary reflects an independent review of the literature and does not represent a policy statement of NCI or the National Institutes of Health (NIH).

Board members review recently published articles each month to determine whether an article should:

- be discussed at a meeting,
- be cited with text, or
- replace or update an existing article that is already cited.

Changes to the summaries are made through a consensus process in which Board members evaluate the strength of the evidence in the published articles and determine how the article should be included in the summary.

The lead reviewers for Mistletoe Extracts are:

- John A. Beutler, PhD (National Cancer Institute)
- Channing J Paller, MD (Johns Hopkins Hospital)

Any comments or questions about the summary content should be submitted to Cancer.gov through the Web site's Contact Form. Do not contact the individual Board Members with questions or comments about the summaries. Board members will not respond to individual inquiries.

**Levels of Evidence**

Some of the reference citations in this summary are accompanied by a level-of-evidence designation. These designations are intended to help readers assess the strength of the evidence supporting the use of specific interventions or approaches. The PDQ Cancer Complementary and Alternative Medicine Editorial Board uses a formal evidence ranking system in developing its level-of-evidence designations.

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