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Use of Mistletoe Extract in Cancer

By Melinda Ring, MD, and Marjorie Alschuler, PhD

WHEN ACTRESS SUZANNE SOMERS ANNOUNCED HER DECISION TO use mistletoe in place of conventional chemotherapy to treat her breast cancer, many thought her decision was unique. But in fact, mistletoe is among the most widely used non-traditional cancer treatments in Europe.[1] It's estimated that more than $30 million per year is spent on mistletoe extracts in Germany alone. A survey of 200 German physicians showed that almost 45% prescribed this herb to their cancer patients.[2]

Proponents claim it stimulates the immune system, promotes cancer cell reversion to more differentiated forms, improves overall well-being, and may extend survival in certain cancers.[3] Additionally, it is used for cancer prevention in high-risk patients, such as those with ulcerative colitis, cervical dysplasia, papillomatosis of the bladder, and intestinal polyposis. Mistletoe also is being investigated for utility in AIDS patients, and deserves a closer look for cancer.

Introduction

Complementary and alternative medicine (CAM) treatments are used extensively by cancer patients. In 1998, a systematic review of 26 surveys from 13 countries found an average prevalence of use of 31% in this patient population; other studies have suggested rates approaching 60-70%.[4] Herbal remedies, homeopathy, and relaxation therapies are employed most frequently. In one investigation into CAM's popularity, cancer patients cited a desire to "leave no stone unturned" in searching for a cure, a belief in the mind-body connection, a preference for a holistic approach, and media publicity.[5]

History

Mistletoe's history as a medicinal spans centuries. It reportedly was cut from trees with a golden sickle by Celtic druids for use as a panacea. Hippocrates recommended mistletoe for disorders of the spleen. In the 16th century, mistletoe was used to treat epilepsy and other nervous system diseases. Subsequent applications included hypertension, tachycardia, headache, menopausal symptoms, infertility, and arthritis.

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INSIDE

Interest in mistletoe as a cancer therapy developed in the 1920s under the rubric of anthroposophy, a scientific framework founded by the Austrian philosopher Rudolf Steiner, PhD. Anthroposophy blends spiritual and scientific principles and applies them to healing practices, with a strong focus on cancer therapies. According to anthroposophical theory, there are four distinct classes of natural forces: *materia*, *forma*, *anima*, and *geist*—roughly translated as physical body, life, soul, and spirit. Imbalances of these forces lead to human disease; treatment aims to restore the equilibrium by activating the patient's self-healing capacities.

Steiner proposed that the parasitic nature and other growth characteristics of mistletoe made it uniquely valuable in the fight against the parasitic growth of cancer. He applied the homeopathic principles of "like cures like" and dilutional potentization (the more diluted the substance, the greater its potency) and developed mistletoe preparations for cancer patients.

At the present time mistletoe extracts are used most extensively by physicians in anthroposophic clinics in Switzerland and Germany. Since the establishment of the clinics in the 1920s, more than 80,000 patients have been treated with regimens that include homeopathic extracts, dietary manipulation, and movement therapies.

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Laboratory Evidence/Active Constituents

Since Steiner popularized mistletoe extract, research to identify active components and determine anticancer properties has proliferated. Mistletoe, like some other plants, does activate the immune system in vitro. Activation of NK-cells, monocytes/macrophages, and T-cells (especially T-helper cells) and stimulation of cytokine release, including interleukin-1, interleukin-6, and tumor necrosis factor, have been demonstrated.[6] Studies using cell systems have identified effects such as increased DNA stability and inhibition of cell growth.[3]

The lectin viscumin (also known as mistletoe lectin I [ML-I] or VAL) and protein viscotoxin are the two major active components in mistletoe preparations.[3] Lectins are glycoproteins that can bind sugar portions on cell surfaces. Actions of viscumin include: interference with intracellular protein synthesis, stimulation of cytokine production, and activation of leukocytes. Additionally, viscumin may influence the processes of metastasis and apoptosis. Viscotoxin works primarily by damaging the cell membrane and inducing cell necrosis, rather than immune system modulation. Other biologically active constituents under investigation include polysaccharides and alkaloids.

Clinical Evidence

Despite the long history of mistletoe use, data from human studies are limited and often of poor quality. Problems include the use of different mistletoe preparations or doses, and the use of immune system effects rather than tumor response or survival as an endpoint.

A review article in 1994 evaluated 11 controlled clinical trials, all of which were originally published in German.[7] Most of the trials enrolled patients with a single type of cancer, including colorectal, gastric, lung, breast, and female genital cancer. Survival duration was the primary endpoint in all cases. Although 10 trials reported prolonged survival, significant flaws limited the validity of the results. The one trial found to have a satisfactory design failed to show any difference in lung cancer survival with mistletoe extract compared to placebo.

Subsequent randomized studies reported improvement in quality of life (as measured by standard questionnaires) in breast cancer (n = 25) and glioma (n = 38) patients when mistletoe extract was added to their treatment regimens.[8,9] No change in disease-free or overall survival was noted. Similarly, 16 patients with stage III-IV pancreatic cancer enrolled in a phase I/II trial showed no partial or complete remissions, but quality-of-life scores stabilized in the treatment group.[10] A phase II trial involving 14 patients with stage IV kidney cancer found no survival advantage with mistletoe extract.[11]

Within the past year, several large prospective randomized controlled clinical trials were published in English-language journals. Steur-Vogt et al studied the clinical effectiveness of adjuvant mistletoe extract in 477 patients with head and neck squamous cell cancer.[12] The patients first were divided into two groups after TNM (tumor, node, metastasis) staging, either undergoing surgery alone (n = 202) or surgery combined with postoperative radiotherapy (n = 275). Both sets then were randomized to standard treatment alone (control group), or standard treatment plus Eurixor, an extract standardized to ML-I. Statistical analysis after an average of four years of follow-up showed no significant improvement in disease-free survival or tumor-related mortality. Additionally, no changes were noted in cellular immunity as measured by lymphocyte subsets or quality-of-life scores, as assessed with the European Organization for Research and Treatment of Cancer Quality of Life Score 30 instrument. The investigators concluded that Eurixor cannot be recommended as adjuvant treatment in head and neck cancer patients.

Eggermont et al studied 830 patients with high-risk melanoma, defined as a primary tumor greater than 3 mm diameter with negative regional lymph nodes or any size primary tumor with 1-2 positive regional nodes and no distant metastases.[13] After potentially curable surgery, patients were randomized to receive adjuvant treatment for one year with subcutaneous injections of interferon-alpha, interferon-gamma, or IscadorM (a mistletoe preparation), or no further treatment. Analysis after six years of follow-up showed no prolongation in time to tumor recurrence or improvement in overall survival with any of the tested adjuvant treatments.

In contrast to these results, an extensive cohort study conducted in Germany found a positive effect from mistletoe treatment.[14] Non-randomized and randomized matched pairs were studied in the context of a prospective, long-term epidemiological study of cancer survival involving 10,226 patients. A total of 1,668 of these patients had used a mistletoe extract. In the non-randomized study of 396 matched pairs, mean survival time was 40% longer in the mistletoe group (4.23 years) compared to control (3.05 years; $P < 0.001$). The two randomized, matched-pair studies supported this finding. Survival time was prolonged in all cancer types studied: carcinoma of the colon, rectum, or stomach; breast carcinoma with and without axillary or remote metastases; and small cell or non-small cell bronchogenic cancer. The research also found that Iscador use tended to improve patient psychosomatic self-regulation, or ability to achieve a sense of well-being and control in a stressful situation.

Preparation/Administration

Mistletoe is a semi-parasitic evergreen bush, which grows on deciduous trees such as oak, pine, elm, and apple.[15] Although mistletoe species are found in the United States (*Phoradendron leucarpum*) and Korea (*Viscum album coloratum*), only the European *Viscum album* Loranthacea is employed in cancer preparations.

Iscador is the trade name of the most commonly available extract of European *Viscum album*, manufactured by Weleda AG in Switzerland and West Germany. It is distributed in the United States by Weleda Inc., as a homeopathic remedy with the brand name Iscar.

Iscador and Iscar are produced by taking an aqueous extract of the whole mistletoe plant. The extract then is fermented with the bacterium *Lactobacillus plantarum*, mixed, filtered for bacteria removal, standardized, and packaged into ampules. Iscador is identified further by the type of host tree: IscadorM, apple tree; IscadorP, pine tree; IscadorQ, oak tree; and IscadorU, elm tree.

Other mistletoe formulations, available under the trade names Helixor, Eurixor, Isorel, Plenosol, Vysorel, and ABNOB Aviscum, may be fermented or unfermented, standardized to one of the purported active constituents rather than including the whole plant, or modified by the addition of homeopathic doses of metals, such as mercury, silver, or copper.

Iscador typically is injected subcutaneously into the abdominal wall, preferably near the tumor site. Some anthroposophic practitioners inject the substance directly into the tumor. The drug regimen is individualized for patients following a protocol established by Steiner, in which escalating doses are given 3-7 times weekly over several weeks to months. Maintenance-phase injections may be prescribed on an individual basis.

Safety/Adverse Effects

Side effects related to mistletoe preparations administered subcutaneously have been minimal and non-life threatening in clinical studies. Injections commonly lead to localized soreness and inflammation, with headache, fever, and chills.[16] These reactions are viewed favorably by anthroposophic practitioners as signs of immune system stimulation. Transient episodes of gingivitis, eosinophilia, and elevations in serum urea nitrogen and creatinine also may occur.[17] Toxic ingestion of mistletoe plants and berries can lead to seizures, bradycardia, blood pressure fluctuations, emesis, and death.

Regulation

Since 1999 Iscar has been listed with the U.S. Food and Drug Administration in accordance with requirements for homeopathic medicines. It is available by

prescription only. In Germany, mistletoe remedies have the status of a biological standard therapy.

Conclusion

Extensive laboratory evidence supports mistletoe's biological activity and potential benefit to oncology patients. However, human studies to determine whether this activity translates into clinically relevant effects remain inconclusive. In the past few years, several well-designed studies were conducted, with conflicting results.

Recommendation

Given the favorable toxicity profile and potential utility of aqueous *Viscum album* abstracts, further research is warranted. Oncology patients should be cautioned that mistletoe extracts are being investigated as an adjuvant treatment, and are not intended to supplant standard medical therapy. ❖

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References

1. Bussing A. Mistletoe: A story with an open end. *Anti-Cancer Drugs* 1997;8(suppl):S1-S2.
2. Munstedt K, et al. Oncologic mistletoe therapy: Physician's use and estimation of efficacy [in German]. *Dtsch Med Wochenschr* 2000;125:1222-1226.
3. Kaegi E. Unconventional therapies for cancer: 3. Iscador. Task Force on Alternative Therapies of the Canadian Breast Cancer Research Initiative. *CMAJ* 1998;158:1157-1159.
4. Ernst E, Cassileth BR. The prevalence of complementary/alternative medicine in cancer. A systematic review. *Cancer* 1998,83:777-782.
5. Ernst E. Mistletoe for cancer? *Eur J Cancer* 2001;37: 9-11.
6. Becker H. Botany of European mistletoe (*Viscum album* L.). *Oncology* 1986;43(suppl 1):2-7.
7. van Wely M, et al. Toxicity of a standardized mistletoe extract in immunocompromised and healthy individuals. *Am J Ther* 1999;6:37-43.
8. Gorter RW, et al. Tolerability of an extract of European mistletoe among immunocompromised and healthy individuals. *Altern Ther Health Med* 1999;5: 37-44, 47-48.
9. Stein GM, et al. Mistletoe in immunology and the clinic (short review). *Anticancer Res* 1998;18: 3247-3249.
10. Kleijnen J, Knipschild P. Mistletoe treatment for cancer: Review of controlled trials in humans. *Phytomedicine* 1994;1:255-260.
11. Heiny BM, Beuth J. Mistletoe extract standardized for the galactoside-specific lectin (ML-1) induces beta-endorphin release and immunopotentiation in breast cancer patients. *Anticancer Res* 1994;14:1339-1342.
12. Lenartz D, et al. Survival of glioma patients after complementary treatment with galactoside-specific lectin from mistletoe. *Anticancer Res* 2000;20(3B):2073-2076.
13. Friess H, et al. Treatment of advanced pancreatic cancer with mistletoe: Results of a pilot trial. *Anticancer Res* 1996;16:915-920.
14. Kjaer M. Mistletoe (Iscador) therapy in stage IV renal adenocarcinoma. A phase II study in patients with measurable lung metastases. *Acta Oncol* 1989;28: 489-494.
15. Steuer-Vogt MK, et al. The effect of an adjuvant mistletoe treatment programme in resected head and neck cancer patients: A randomised controlled clinical trial. *Eur J Cancer* 2001;37:23-31.
16. Eggermont AM, et al. European Organization for Research and Treatment of Cancer Melanoma Group trial experience with more than 2,000 patients, evaluating adjuvant treatment with low or intermediate doses of interferon alpha-2b. In: *Educational Book from the 37th Annual Meeting of the American Society of Clinical Oncology.* Available at http://www.asco.org.
17. Grossarth-Maticek R, et al. Use of Iscador, an extract of European mistletoe (*Viscum album*), in cancer treatment: Prospective nonrandomized and randomized matched-pair studies nested within a cohort study. *Altern Ther Health Med* 2001;7:57-66, 68-72, 74-76.

The Use of Psyllium and Soy for Hypercholesterolemia

By Susan T. Marcolina, MD

HYPERLIPIDEMIA IS A MAJOR RISK FACTOR FOR CORONARY heart disease (CHD), the leading cause of death among American adults.[1,2] In the United States, 32% of adult men and 27% of adult women have hyperlipidemia according to the National Cholesterol Education Program (NCEP).[3] Because diet is the main environmental determinant of plasma lipid concentrations, dietary modification is an important therapeutic tool whereby physicians can alter patient risk profiles.

Current initial treatment for hyperlipidemia recommended by the Adult Treatment Panel III include the

following therapeutic lifestyle changes: 1) reduced intakes of saturated fats (fewer than 7% of total calories) and cholesterol (less than 200 mg/d); 2) use of therapeutic dietary additions, such as plant stanols/sterols (2 g/d) and increased soluble dietary fiber intake (10-25 g/d); 3) weight reduction; and 4) increased physical activity.[4] Many patients need additional cholesterol lowering beyond what can be achieved with these interventions. Lipid-lowering medications, although efficacious in reducing serum cholesterol and the incidence of CHD, are expensive and can cause severe adverse reactions.[5]

Dietary measures, such as addition of soluble fiber and substitution of soy protein for meat and dairy products, can help patients achieve lower cholesterol levels. On a population-wide basis, each 1% reduction in serum cholesterol can reduce heart disease mortality by 2%.[6] These interventions, therefore, can provide valuable additions to a patient's cholesterol-lowering menu.

Table 1

Cost of common psyllium-containing fiber supplements

Product	Single Dose	Cost per Dose
Metameucil	1 tsp (3.4 g)	$0.09
Konsyl	½ tsp (3.4 g)	$0.14
Yerba Prima Psyllium husk powder	1 tsp (3.5 g)	$0.13
Nature's Way Psyllium husk seed	5 capsules (3.1 g)	$0.45
Nature's Herbs Psyllium husk	5 capsules (2.8 g)	$0.45

Adapted from: Bennett WG, et al. Benefits of dietary fiber: Myth or medicine? *Postgrad Med* 1996;99:169-175.

Dietary Fiber

The U.S. population, with one of the lowest dietary fiber intakes in the world, has much to gain from supplementation.[7] Dietary fibers are the complex carbohydrates in fruits, vegetables, grains, nuts, and legumes that human digestive enzymes cannot break down. Soluble dietary fibers, shown to have cholesterol-lowering effects, include pectins, gums, psyllium, and algal polysaccharides; insoluble fibers include cellulose, lignin, and hemicellulose.[8] Psyllium is a source of soluble fiber derived from the husks of blond psyllium seed, *Plantago ovata*, cultivated primarily in India.[9] Table 1 lists some psyllium-containing fiber supplements.

Mechanism of Action

Two major hypotheses have been presented to explain the lipid-lowering action of psyllium. In the first, soluble fiber physically entraps bile acids, resulting in increased fecal loss.[10,11] The second theory postulates that soluble fiber produces a decrease in cholesterol absorption and bile acid reabsorption by physical disruption of intraluminal micellar formation. In both mechanisms, interruption of the enterohepatic circulation causes increased conversion of cholesterol into newly synthesized bile acids in the liver. This reduction in cholesterol biosynthesis leads to an up-regulation of the low-density lipoprotein (LDL) receptor. This in turn leads to an enhanced plasma LDL uptake and reduced serum LDL-cholesterol (LDL-C) and total cholesterol levels.[12]

Soluble fibers have other lipid effects. They are fermented by colonic bacteria to short-chain fatty acids, which suppress cholesterol synthesis by limiting the action of HMG-CoA reductase, the enzyme that catalyses the rate-limiting step of cholesterol biosynthesis.[13] Soluble fiber decreases gastrointestinal lipid and cholesterol absorption and serum insulin secretion, and increases peripheral insulin sensitivity.[14] Marckmann et al showed in an eight-month study of healthy young men that a low-fat, high-fiber diet increases fibrinolysis.[15]

Watts et al demonstrated that 27 men with CHD who were treated with a low-fat, high-fiber diet (about 5 g pectin per day) showed improvement in angiographic patency of stenosed segments and a significant decrease in clinical cardiac events in comparison to controls.[16]

The mechanism by which soybean products lower cholesterol levels is not certain. Huff et al suggest that turnover of very low-density lipoprotein apoprotein (apo) B is increased in humans when soy protein is substituted for meat and dairy protein.[17] Lovati et al noted an eightfold increase in the LDL-receptor activity of monocytes in human subjects who regularly consumed soy products compared to those eating control diets.[18]

Regulation

In February 1998, the Food and Drug Administration (FDA) authorized manufacturers of foods containing soluble fiber from psyllium seed husk (PSH) to claim a benefit for the treatment of CHD. Foods carrying this health claim must provide 1.7 g/serving of soluble fiber from PSH.[19]

In October 1999, the FDA authorized the use of health claims about the reduction of CHD risk on the labeling of foods containing soy protein. Based on the results of clinical studies, the FDA recommends daily ingestion of 25 g or more of soy protein to achieve optimal reduction in total cholesterol and LDL-C levels.[20]

Clinical Studies

Anderson et al published a meta-analysis that included five published studies of the hypocholesterolemic effects of 10.2 g psyllium per day adjunctive to an

American Heart Association (AHA) Step I diet.[9] All patients in these studies had been on the low-fat diet for a lead-in of 8-12 weeks and were randomized to their specific groups. Duration of treatment was from eight to 12 weeks. All studies had a cellulose placebo. Psyllium was associated with significant reductions in serum total cholesterol and LDL-C concentrations, total to high-density lipoprotein-cholesterol (HDL-C) ratios, and apoB/apoA-1 ratio compared with placebo. Psyllium intake did not significantly affect serum HDL-C concentrations. No significant differences were found in serum triglyceride (TG) concentrations between the psyllium and placebo groups.

Jensen et al conducted a six-month, double-blind, randomized, placebo-controlled, parallel comparison of 15 g/d of a supplemental, water-soluble dietary fiber (WSDF), which was a mixture of psyllium, pectin, guar gum, and locust bean gum with an inactive WSDF control (acacia gum).[21] Changes in the mean plasma lipids and lipoprotein measures did not differ significantly from baseline to each of the follow-up periods for the control group. For the treated group, the mean plasma total cholesterol concentration declined by 6.4% and LDL-C declined by 10.5% ($P < 0.05$); these reductions were sustained throughout the study period. Mean plasma HDL-C and TG concentrations did not significantly change over the course of the study. The TG levels were quite variable and tended to be higher over the course of study in the treatment group. All of the subjects maintained their typical eating, physical activity, and medication patterns throughout the study.

Anderson et al performed a meta-analysis that included 29 articles on the effects of ingesting 31-47 g of soy protein on serum cholesterol concentrations.[22] All studies were controlled with a parallel or crossover design. In the majority of the studies, dietary fat content was similar in the control and experimental groups. The use of soy in the experimental group diet caused a net decrease in total cholesterol of 9.3%, a net decrease in LDL-C of 12.9%, a net increase in HDL-C of 2.4%, and a net decrease in TG of 10.5%. The initial serum cholesterol level was the most significant predictor of change.

Wong et al evaluated the effects of the substitution of approximately 50 g/d of soy protein for animal protein in a NCEP Step 1 diet with a fixed fiber content of 25 g/d and similar amounts of saturated, monounsaturated, and polyunsaturated fatty acids.[23] Thirteen hypercholesterolemic and 13 normocholesterolemic men were enrolled in this randomized, two-part crossover study with a washout of 10-15 weeks between diets. All participants completed the study. The investigators found that the cholesterol-lowering effect of the soy protein diet was independent of age, weight, pretreatment plasma lipid concentrations, and sequence of dietary treatment. The soy protein diet was associated with a statistically significant decrease in the plasma LDL-C concentrations of 6% ($P = 0.029$), as well as a decrease of 11% in the ratio of plasma LDL-C to HDL-C ($P = 0.005$).

Lewis et al found the effects of dietary saturated fat reduction and fiber supplementation to be additive in causing a decrease in serum total cholesterol of 29.2%, a decrease in LDL-C of 34.5%, and a decrease in serum TG of 20.8%, compared with Western diet controls.[24]

Adverse Reactions

Anderson et al assessed the safety of psyllium by pooling data from 19 clinical studies using psyllium. The amounts of psyllium varied from 5.1 to 20.4 g/d across the studies. A total of 966 patients were treated with psyllium. The most common symptoms presented more frequently in treated patients and included flatulence and bloating. No serious or unexpected psyllium-related adverse events occurred.

Psyllium always should be taken with at least 8 ounces of water per teaspoon.[9] Psyllium-containing products should not be given to persons with gastrointestinal strictures or impaired gastrointestinal motility.[25] Psyllium should be avoided by persons with known or suspected allergy; allergy symptoms include allergic rhinitis, conjunctivitis, urticaria, and asthma. Psyllium is safe to use during pregnancy and lactation when taken with adequate amounts of fluid.

The most common side effects after introduction of soy protein to a soy-naïve diet are flatulence, bloating, abdominal cramping, and increased stool frequency, all of which often resolve with time and gradual re-introduction.

Conclusion

Multiple dietary manipulations, such as the addition of soluble fiber supplements and soy proteins, contribute significantly, individually, and in the aggregate to cholesterol lowering and may alleviate the need for pharmacotherapy in patients at risk for CHD. Physicians need to tailor carefully the interventions as appropriate to the patient's clinical situation.

Recommendation

Psyllium and soy protein are useful adjuncts for patients on a low-fat, AHA diet who have not reached their goal cholesterol level. They can be incorporated into a healthy lifestyle, which includes daily exercise and weight reduction to decrease cholesterol levels, specifically LDL-C.

Table 2

Examples of good dietary sources of fiber

Food	Serving	Fiber Content	Soluble Fiber
Kidney beans	½ cup	4.5 g	1.0 g
Spinach	½ cup	2.0 g	0.5 g
Potato with skin	1 medium	4.0 g	1.0 g
Apple	1 medium	3.0 g	0.5 g
Oatmeal	¾ cup	3.0 g	1.0 g

Source: American Dietetic Association. Available at: www.eatright.org/nfs/nfs88.html.

The recommended daily intake for lowering cholesterol is 10.2 g of psyllium seed husk, or approximately 7 g of soluble fiber. In adults, a single serving size of 1.7 g should be consumed with at least 8 ounces of water and can be increased gradually to four times daily to produce the cholesterol-lowering effect.[20] Consumption of soluble fiber supplements with meals is important for cholesterol-lowering efficacy.[22] Because it may interfere with the absorption of other medications, particularly oral anticoagulants, PSH should be taken either one hour before or three hours after medications.

Soy protein should be introduced gradually to the diet to avoid side effects. A gradual increase to 25 g of soy protein daily over several weeks can produce the desired cholesterol-lowering effects.[21] Tables 2 and 3 summarize common sources of soy protein and fiber. ❖

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References

1. Marmot MG. Epidemiological basis for the prevention of coronary heart disease. *Bull World Health Organ* 1979;57:331-347.
2. Keys A. *Seven Countries: A Multivariate Analysis of Death and Coronary Heart Disease.* Cambridge, MA: Harvard University Press; 1980.
3. Adult Treatment Panel II. National Cholesterol Education Program: Second Report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. *Circulation* 1994;89:1333-1445.
4. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-2497.
5. FDA Talk Paper. Bayer Voluntarily Withdraws Baycol. Available at: http://www.fda.gov/bbs/topics/answers/2001/ans01095.html. Accessed Sept. 2, 2001.

Table 3

Examples of good dietary sources of soy protein

Foods	Serving	Soy Content
Soy flour	¼ cup	8 g
Soy breakfast links	2 links	6.5 g
Soy burger	1 patty	10 g
Green soybeans	½ cup	7 g
Soynut non-dairy butter	2 tbsp	8 g

Source: Soy Protein Partners. *2001 Soyfoods Guide.* Available at: www.soyfoods.com/SoyfoodsGuide.pdf.

6. Lipid Research Clinics Program. The lipid research clinics coronary primary prevention trial results. 1. Reduction in incidence of coronary heart disease. *JAMA* 1984;251:351-364.
7. Spiller GA, ed. CRC *Handbook of Dietary Fiber in Human Nutrition.* 2nd ed. Boca Raton, FL: CRC Press; 1993.
8. Chu WW, et al. Dietary fiber and coronary artery disease. *WMJ* 2000;99:32-36.
9. Anderson JW, et al. Cholesterol-lowering effects of psyllium intake adjunctive to diet therapy in men and women with hypercholesterolemia: Meta-analysis of 8 controlled trials. *Am J Clin Nutr* 2000;71:472-479.
10. Everson GT, et al. Effects of psyllium hydrophilic mucilloid on LDL-cholesterol and bile acid synthesis in hypercholesterolemic men. *J Lipid Res* 1992;33: 1183-1192.
11. Matheson HB, et al. Cholesterol 7 alpha-hydroxylase activity is increased by dietary modification with psyllium hydrocolloid, pectin, cholesterol and cholestyramine in rats. *J Nutr* 1995;125:454-458.
12. Story JA. The role of dietary fiber in lipid metabolism. *Adv Lipid Res* 1981;18:229-246.
13. Anderson JW. Short-chain fatty acids and lipid metabolism. In: Cummings JH, et al, eds. *Physiological and Clinical Aspects of Short Chain Fatty Acids.* New York: Cambridge University Press; 1995:509-523.
14. Jenkins DJ, et al. Effect on blood lipids of very high intakes of fiber in diets low in saturated fat and cholesterol. *N Engl J Med* 1993;329:21-26.
15. Marckmann P, et al. Favorable long-term effect of a low-fat/high-fiber diet on human blood coagulation and fibrinolysis. *Arterioscler Thromb* 1993;13:505-511.
16. Watts GF, et al. Effects on coronary artery disease of lipid-lowering diet or diet plus cholestyramine in the St. Thomas' Atherosclerosis Regression Study (STARS). *Lancet* 1992;339:563-569.
17. Huff MW, et al. Turnover of very low-density lipoprotein-apoprotein B is increased by substitution of soybean protein for meat and dairy protein in the diets of

hypercholesterolemic men. *Am J Clin Nutr* 1984;39: 888-897.
18. Lovati MR, et al. Soybean protein diet increases low density lipoprotein receptor activity in mononuclear cells from hypercholesterolemic patients. *J Clin Invest* 1987;80:1498-1502.
19. FDA Talk Paper. FDA Allows Foods Containing Psyllium to Make Health Claim on Reducing Risk of Heart Disease. Available at: http://www.cfsan.fda.gov/~1rd/tpsylliu.html. Accessed July 17, 2001.
20. FDA Talk Paper. FDA Approves New Health Claim for Soy Protein and Coronary Heart Disease. Available at: http://www.cfsan.fda.gov/~1rd/tpsoypr2.html. Accessed Aug. 28, 2001.
21. Jensen CD, et al. Long-term effects of water-soluble dietary fiber in the management of hypercholesterolemia in healthy men and women. *Am J Cardiol* 1997;79:34-37.
22. Anderson JW, et al. Meta-analysis of the effects of soy protein intake on serum lipids. *N Engl J Med* 1995; 333:276-282.
23. Wong WW, et al. Cholesterol-lowering effect of soy protein on normocholesterolemic and hypercholesterolemic men. *Am J Clin Nutr* 1998;68(6 Suppl): 1385S-1389S.
24. Lewis B, et al. Towards an improved lipid-lowering diet: Additive effects of changes in nutrient intake. *Lancet* 1981;2:1310-1313.
25. Shulman LM. Perdiem causing esophageal obstruction in Parkinson's disease. *Neurology* 1999;52:670-671.
26. Graedon J, Graedon T. Guide to Herbal Therapies—Psyllium. In: Graedon J, Graedon T, eds. *The People's Pharmacy Guide to Home and Herbal Remedies.* New York: St. Martin's Press; 1999.

Flaxseed and Flaxseed Oil in the Management of Hypercholesterolemia

PART I OF A SERIES ON FLAXSEED

By Philippe O. Szapary MD, and LeAnne T. Bloedon, MS, RD

THE POPULARITY OF FLAXSEED STEMS FROM THE FACT that it contains three important constituents (fiber, alpha linolenic acid, and lignans) that have been implicated in the prevention and treatment of chronic diseases ranging from cardiovascular disease to cancer prevention and inflammatory disorders.

The best evidence to date suggests that flaxseed products improve cardiovascular risk factors primarily by modestly improving lipid profiles. Flaxseed's antiarrhythmic, antiplatelet, antioxidant, and hypoglycemic potential will be covered in a separate article.

History

Evidence of flaxseed cultivation can be found as early as 6000 BC in Eastern Turkey, where it was used to make linen.[1] During the past millennia, components of flaxseed have been used for a variety of purposes. Traditionally, the oil, known as linseed oil, is used as a drying agent in paint and varnish.

Composition and Pharmacology

Flax (*Linum usitatissimum*) is a blue flowering crop that produces small, flat seeds that range in color from golden yellow to reddish brown. Flaxseed commonly is found as whole seed, flaxseed powder, or flaxseed oil. Whole flaxseed contains 41% fat, 28% dietary fiber, and 21% protein, in addition to minerals, vitamins, and to a lesser extent, carbohydrates.[2]

Flaxseed oil is comprised of 73% polyunsaturated fatty acids, 18% monounsaturated fatty acids, and 9% saturated fatty acids, making it a low saturated fat food.[2] Flaxseed oil is unique in that it is the richest known source of alpha-linolenic acid (ALA), a compound with cardioprotective effects.[3]

The dietary fiber portion of flaxseed contains both insoluble and soluble fibers. The lipid-lowering properties of flaxseed fiber are attributed to mucilage, the soluble fiber portion. Although fiber is not digestible by humans, it affects absorption of fat and metabolism of food components by altering transit time.

Flaxseed contains several lignans, which are phytoestrogens, and is the richest source of the main mammalian lignan precursor, secoisolariciresinol (SDG).[4]

Mechanism of Action

The fiber portion of flaxseed may lower serum cholesterol by a number of potential mechanisms, including enhanced gastric emptying, altered transit time, interference with bulk-phase diffusion of fat, and increased excretion of bile acids.[5]

Evidence also suggests that the lignans precursor SDG may directly lower serum cholesterol.[6] It has been hypothesized that lignans may be able to lower serum cholesterol through modulation of enzymes involved in cholesterol metabolism, including 7α-hydroxylase and acyl CoA cholesterol transferase.[7]

Table

Comparison of commercially available flaxseed and flaxseed oil products

Product	a -linolenic Acid Content	Fiber per Serving	Lignans (Yes/No)	Calories	Retail Pricing
Whole flaxseed	2.2 g/tbsp	3.3 g/tbsp	Yes	59/tbsp	$0.99/lb
Flaxseed powder	5.4 g/tbsp	3.0 g/tbsp	Yes	40/tbsp	$5.99/8 oz
Flaxseed oil	7.5-10.5 g/tbsp	0	No	130/tbsp	$5.99-8.59/oz
Linseed bread (The Baker)	Not listed	5 g (slice)	Yes	100/slice	$2.99/17.6 oz (8 slices)
Flax Plus cereal	600 mg/serving	5 g	Yes	120 per ¾ cup	$2.99/13.25 oz

Sources: U.S. Department of Agriculture Nutrient Database for Standard Reference; and online retailers.

Animal Studies

Several animal studies have focused on the question of whether flaxseed, or portions of flax, can improve serum lipids. Weanling rats fed 20% and 40% flaxseed for 90 days produced significantly lower serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels than rats fed a diet devoid of flaxseed.[8] In rabbits, adding purified SDG (15 mg/kg) to an atherogenic diet for eight weeks reduced TC and LDL-C by 33% and 35%, respectively, while it remarkably increased high-density lipoprotein cholesterol (HDL-C) by more than 140% in as few as four weeks.[6]

When the authors examined the extent of atherosclerotic burden in the aorta, the SDG-treated group had significantly smaller plaques and the lesions were distributed over a smaller area compared to the control group. The same group of authors found that defatted flaxseed (2-3% ALA, but similar in lignan content to traditional flaxseed) similarly reduced TC and LDL-C in rabbits fed an atherogenic diet for eight weeks when compared to controls, but had no effect on HDL-C.[9]

Human Studies

To identify the majority of human studies on the lipid effects of flaxseed, we performed a systematic search of the following databases: MEDLINE, BIOSIS Previews, CINHAL, Cochrane Collaboration Database, and CAM on PubMed. We used the MeSH headings "flax," "alpha linolenic acid," "fatty acid, omega-3," "lignans," and "dietary fiber," as well as the search terms "flaxseed" and "linseed." We also hand searched recent relevant review articles for additional references. Using this strategy, we identified 353 articles and book chapters. The description below highlights the information specifically on the lipid-lowering effects of flaxseed products.

The bulk of the evidence from nine clinical trials suggests that flaxseed or flaxseed powder can modestly reduce TC and LDL-C by 5-15%, without an effect on HDL-C or triglycerides (TG).[10] Flaxseed oil given alone in large doses (60 mL) can modestly reduce TG.[11] One double-blind, randomized controlled trial of 38 moderately hyperlipidemic postmenopausal women (average LDL-C: 158 mg/dL) found that 38 g of whole flaxseed baked into muffins can reduce LDL-C by 14.7% compared to a sunflower seed control muffin.[12] There were no effects on TG or HDL-C, but interestingly, lipoprotein (a), a newer marker of coronary heart disease, was mildly but consistently reduced by 7.4%.

In normolipidemic volunteers, Cunnane et al showed that consuming a large amount of ground flaxseed daily (50 g/d in two muffins) reduced LDL-C by 8% at two weeks, and increased bowel movements by 30%.[13] These same investigators found similar results using defatted flaxseed muffins in 29 hyperlipidemic subjects over six weeks.[14] These results imply that the hypolipidemic effect of flaxseed is independent of ALA content.

We identified six studies that specifically evaluated the lipid effects of flaxseed oil with doses of ALA ranging from 9.2 to 38 g/d. Only the study using the highest dose of ALA, equivalent to 60 mL (about 4 tbsp/d) of flaxseed oil, found a TG-lowering effect of 25%, without changes in TC, LDL-C, or HDL-C.[15] This decrease in fasting serum TG is comparable to that obtained with marine fish oil, except that the fish oils produce the TG-lowering effect at much lower doses.

Adverse Effects and Drug Interactions

The Food and Drug Administration allows inclusion of up to 12% (by weight) flaxseed in foods, but flaxseed and cold-pressed flaxseed oil have not attained GRAS (Generally Recognized As Safe) status.

There are no known or suspected adverse effects or interactions with flaxseed oil; however, the fiber and lignan components of flax may cause some problems. Human studies using up to 50 g flaxseed per day for up to one month revealed no adverse effects and that flaxseed was well-tolerated in one study.[13] This same study noted a 30% increase in bowel movements with

this flaxseed supplementation. Thus, clinicians may want to avoid recommending flaxseed for patients with a history of bowel obstruction, or in some patients with irritable bowel syndrome. Additionally, the small whole seeds could theoretically precipitate a bout of diverticulitis and probably should be avoided by patients with known diverticular disease. Grinding the seeds should remove this theoretical risk.

There is no published evidence concerning the safety of flax in pregnancy or lactation. However, flax has potential hormonal effects, which may result from bioactive lignans binding to estrogen receptors. There are no published reports of drug interactions. Because of their fiber content, flaxseed products probably should not be co-administered with prescription drugs to avoid interference with drug absorption.

Studies looking at another class of phytoestrogens, known as isoflavones, have found that soy isoflavones, genistein and daidzein, cause chromosomal mutations and DNA strand breaks in vitro at high concentrations.[2] These genotoxic properties theoretically could increase the risk of neoplasia. Initial studies on lignans from flax reveal no evidence of genotoxicity.[16] However, the issue of whether flaxseed or its components may be carcinogenic or chemoprotective actively is being investigated.

Dietary Sources of Flax

Flaxseed is sold in bulk, and in powder and oil forms. The oil is best used in salad dressings and blended into smoothies. The oil also can be used to sauté foods briefly at medium heat; however, it degrades at high temperatures. The oil becomes rancid quickly when exposed to heat, light, and oxygen, and should be stored in an opaque bottle and refrigerated after opening.

Whole flaxseed can be used in a variety of foods when crunchiness or a nutty flavor is desired. In addition to baking whole flaxseed in breads, muffins, pancakes, waffles, or bagels, it can be sprinkled onto cereal, yogurt, or salads. Grinding seeds in a coffee grinder allows the user to mix it into juices or low-fat milk. Whole flaxseed can be stored for up to one year in a dry place. Ground flaxseed can be stored in the refrigerator for approximately three months; when frozen, ground flaxseed can be preserved for six months or longer.

Both flaxseed powder and oil also are sold as dietary supplements. The oil frequently is sold in either capsule form or as a liquid *(see Table).*

Conclusion

Whole flaxseed and flaxseed powder can modestly reduce LDL-C by 5-10% without affecting HDL-C or TG. Conversely, flaxseed oil does not reliably lower LDL-C, but can reduce TG at high doses. The large amount of flaxseed oil (4 tbsp and 480 calories) needed to reduce TG makes this oil an impractical and highly caloric intervention.

Recommendation

Based on current literature, flaxseed or flaxseed powder can be a useful part of a cholesterol-lowering diet, such as the Therapeutic Lifestyle Changes (TLC) diet, which recently was endorsed by the National Cholesterol Education Program.[17] Like psyllium, adding 2 tbsp/d of flaxseed to a diet low in saturated and trans-fatty acids equally will reduce serum cholesterol; unlike psyllium, however, this dose of flax also will add cardioprotective omega-3 fatty acids, making this grain a very useful part of a heart healthy diet. ❖

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References

1. Judd A. Flax—some historical perspective. In: Cunnane SC, Thompson LU, eds. *Flaxseed in Human Nutrition*. Toronto, CA: American Oil Chemists Society Press; 1995:1-10.
2. Morris D. Essential nutrients and other functional compounds in flaxseed. *Nutrition Today* 2001;36: 159-162.
3. Cunnane SC, et al. High alpha-linolenic acid flaxseed (*Linum usitatissimum*): Some nutritional properties in humans. *Br J Nutr* 1993;69:443-453.
4. Thompson LU, et al. Mammalian lignan production from various foods. *Nutr Cancer* 1991;16:43-52.
5. Kritchevsky D. Fiber effects of hyperlipidemia. In: Cunnane SC, Thompson LU, eds. *Flaxseed in Human Nutrition*. Toronto, CA: American Oil Chemists Society Press; 1995:174-186.
6. Prasad K. Reduction of serum cholesterol and hypercholesterolemic atherosclerosis in rabbits by secoisolariciresinol diglucoside isolated from flaxseed. *Circulation* 1999;99:1355-1362.
7. Sanghvi A, et al. Inhibition of rat liver cholesterol 7-alpha hydroxylase and acetyl CoA:cholesterol aceyl transferase activities by entrodiol and enterolactone. In: Kritchevsky D, ed. *Proceedings of the Symposium on Drugs Affecting Lipid Metabolism*. New York: Plenum Press; 1984:311-322.
8. Ratnayake WMN, et al. Chemical and nutritional studies of flaxseed (variety Linott) in rats. *J Nutr Biochem* 1992;3:232-240.

9. Prasad K, et al. Reduction of hypercholesterolemic atherosclerosis by CDC-flaxseed with very low alpha-linolenic acid. *Atherosclerosis* 1998;136:367-375.
10. Nelson GJ, Chamberlain JG. The effect of dietary alpha-linolenic acid on blood lipids and lipoproteins in humans. In: Cunnane SC, Thompson LU, eds. *Flaxseed in Human Nutrition.* Toronto, CA: American Oil Chemists Society Press; 1995:187-206.
11. Harris WS. n-3 fatty acids and serum lipoproteins: Human studies. *Am J Clin Nutr* 1997;65(5 Suppl): 1645S-1654S.
12. Arjmandi BH, et al. Whole flaxseed consumption lowers serum LDL-cholesterol and lipoprotein(a) concentrations in postmenopausal women. *Nutr Res* 1998; 18:1203-1214.
13. Cunnane SC, et al. Nutritional attributes of traditional flaxseed in healthy young adults. *Am J Clin Nutr* 1995;61:62-68.
14. Jenkins DJ, et al. Health aspects of partially defatted flaxseed, including effects on serum lipids, oxidative measures, and ex vivo androgen and progestin activity: A controlled crossover trial. *Am J Clin Nutr* 1999; 69:395-402.
15. Singer P, et al. A possible contribution of decrease in free fatty acids to low serum triglyceride levels after diets supplemented with n-6 and n-3 polyunsaturated fatty acids. *Atherosclerosis* 1990;83:167-175.
16. Kulling SE, et al. Studies on the genotoxicity of the mammalian lignans enterolactone and enterodiol and their metabolic precursors at various endpoints in vitro. *Mutat Res* 1998;416:115-124.
17. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001;285:2486-2497.

CME Questions

31. Proponents of mistletoe extract for cancer therapy claim that:
a. it stimulates the immune system.
b. it promotes cancer cell reversion to more differentiated forms.
c. it improves overall well-being.
d. it may extend survival in certain cancers.
e. All of the above

32. Which statement regarding the current state of evidence with respect to mistletoe extract and cancer is true?
a. Lab and clinical research argue against any potential benefit.
b. Lab evidence is favorable, but clinical evidence is inconclusive.
c. Lab evidence is negligible, but clinical evidence is uniformly favorable.
d. Lab and clinical evidence strongly favor the use of mistletoe in cancer.

33. Contraindications to the use of psyllium for hyperlipidemia include:
a. partial small bowel obstruction.
b. hypersensitivity to psyllium.
c. esophageal stricture.
d. All of the above

34. Side effects after initiation of soy protein may include:
a. flatulence.
b. bloating.
c. altered bowel habit.
d. All of the above

35. The following statements about flaxseed are correct *except*:
a. flax traditionally has been used to make clothing.
b. flaxseed is the most concentrated source of alpha-linolenic acid.
c. flaxseed should be avoided in patients with constipation.
d. flaxseed contains phytoestrogenic precursors.

36. Which of the following statements about alpha-linolenic acid (ALA) is/are true?
a. ALA has been shown to reduce cholesterol.
b. ALA has been shown to reduce triglycerides.
c. ALA has been shown to have a cardioprotective effect.
d. Both b and c are correct.

With Comments from John La Puma, MD, FACP

Diet, Lifestyle, and Type 2 Diabetes in Women

Source: Hu FB, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med* 2001;345:790-797.

PREVIOUS STUDIES HAVE EXAMINED individual dietary and lifestyle factors in relation to Type 2 diabetes, but the combined effects of these factors are largely unknown.

Hu et al followed 84,941 female nurses from 1980 to 1996; these women were free of diagnosed cardiovascular disease, diabetes, and cancer at baseline. Information about their diet and lifestyle was updated periodically.

A low-risk group was defined according to a combination of five variables: A body-mass index (BMI = weight in kilograms divided by the square of the height in meters) of less than 25 kg/m^2; a diet high in cereal fiber and polyunsaturated fat and low in trans fat and glycemic load (which reflects the effect of diet on the blood glucose level); engagement in moderate-to-vigorous physical activity for at least 30 minutes per day; no current smoking; and the consumption of an average of at least half a drink of an alcoholic beverage per day.

During 16 years of follow-up, 3,300 new cases of Type 2 diabetes were documented. Overweight or obesity was the single most important predictor of diabetes. Lack of exercise, a poor diet, current smoking, and abstinence from alcohol use all were associated with a significantly increased risk of diabetes, even after adjustment for the BMI.

As compared with the rest of the cohort, women in the low-risk group (3.4% of the women) had a relative risk of diabetes of 0.09 (95% confidence interval [CI], 0.05-0.17). A total of 91% of the diabetes cases in this cohort (95% CI, 83-95%) could be attributed to habits and forms of behavior that did not conform to the low-risk pattern.

These findings support the hypothesis that the majority of cases of Type 2 diabetes could be prevented by adopting a healthier lifestyle.

COMMENT

The Nurses' Health Study began in 1976, when 121,700 female nurses 30-55 years of age responded to a questionnaire regarding medical, lifestyle, and other health-related information. Together with the Physicians' Health Study, it is one of the major sources of what we know in epidemiological retrospect about nutrients and disease.

Here, the follow-up rate with respect to the incidence of diabetes in the overall cohort was 97%; the authors used cumulative update methods for dietary intake and physical activity, assessed every two years; BMI and smoking status were updated every two years; and information about alcohol intake was updated in 1984, 1986, and 1990.

The relative risk of diabetes was 38.8 for women with a BMI of 35 kg/m^2 or higher and 20.1 for women with a BMI of 30.0-34.9 kg/m^2, as compared with women who had a BMI of less than 23 kg/m^2. The lowest quintile for exercise (0.5 hours per week) among those with a BMI higher than 30 kg/m^2, promoted diabetes only half as much as 7.0 hours prevented it in women with BMIs lower than 25 kg/m^2. But minimal exercise still was significantly and independently associated with diabetes development. Activities included brisk walking, heavy gardening, heavy housework, vigorous sports, jogging, and "other activities vigorous enough to build up a sweat."

Last year, Chandalia et al (*N Engl J Med* 2000;342:1392-1398) found that a high-fiber diet (total, 50 g; 25 g of soluble fiber and 25 g of insoluble fiber) containing unfortified, high-fiber foods, dropped mean daily preprandial plasma glucose concentrations by 13 mg/dL; total cholesterol concentrations by 6.7% (P = 0.02); triglyceride concentrations by 10.2% (P = 0.02); and very low-density lipoprotein cholesterol concentrations by 12.5% (P = 0.01).

And Field and colleagues (*Arch Intern Med* 2001;161:1581-1586) recently found that women with a BMI higher than 35 kg/m^2 (now considered "severely obese," until they get to 40 kg/m^2, when they are properly diagnosed as "morbidly obese") were 17 times more likely and men were 23 times more likely to develop diabetes than those of normal weight (BMI < 25 kg/m^2). There was a linear dose-response curve.

The harder questions is "What can my patients do to lose weight, keep it off, and prevent diabetes?" The answer is almost as individual as are patients, but here are some guidelines:

1. Diets that exclude whole food groups do not allow patients to maintain any weight lost. Don't recommend them for weight loss.
2. Eating simply, eating slower, and eating sitting down all help.
3. Celebrate small successes. They add up to big ones in the minds of overweight and obese people, who are used to failing at this (though they may be highly successful at many other endeavors).
4. Start with what people can do, and be very specific. Add just one new effort per week. "Eat only foods with a maximum of 3 g of saturated fat per serving today—look on the label," or "Walk four blocks by yourself five of the seven days this week. Do five blocks next week."
5. Be positive, even if you don't feel that way. Patients need it, especially from their doctor.

Recommendation

The authors properly note that excess body fat is the single most important determinant of Type 2 diabetes. Most people do not recognize the connection between overweight or obesity and diabetes. State this clearly to patients at risk, and tell them, specifically, what to do about it. ❖

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