Compounds in Fruits and Vegetables that Protect Against Cancer and Heart Disease: Recent Research

I've published four columns in the past year about physicians closely associated with nutraceuticals. Three columns were devoted to interviews with Stephen A. DeFelice, MD, the "father" of a mainstream initiative to establish a separate, quicker approval track for nutraceuticals. The last column paid tribute to Louis Lasagna, MD, an authority on clinical pharmacology and controlled clinical trials.

Dr. DeFelice coined the term "nutraceutical" in 1989, while searching for a word or sound-bite phrase that embraced foods and food compounds, dietary supplements, herbal remedies, etc., all of them potentially beneficial in prevention and treatment of disease. Through the 1990s, Dr. DeFelice and the non-profit organization he chairs, the Foundation for Innovation in Medicine (FIM), sponsored nutraceutical conferences, hoping to catch the attention of Congress. In 2000, Representative Frank Pallone (D-NJ) introduced the Nutraceutical Research and Education Act (NREA) in the House.

Dr. Lasagna, a member of FIM's board of directors, made memorable presentations at these conferences on consensus of opinion among medical experts and the risks involved in using new drugs.

The only nutraceutical referred to in those four columns was carnitine. Dr. DeFelice had conducted seminal studies on this naturally occurring substance in the mid-1960s, and over the following decades, he has continued to investigate the protective effects of carnitine in the heart and body.

FIM's conferences included presentations on many nutraceuticals. This column reports selectively on studies in the past two years on a number of foods and compounds in food that show promise in preventing and treating major diseases.

Eat Red

Sour cherries and tomatoes are rich in pigments that appear to reduce inflammation linked to hardening of the arteries. Cherry-enriched diets have lowered blood cholesterol and triglycerides in animal studies, according to a study conducted by a team of scientists at the University of Michigan in 2007. One of the authors of this study, Dr. Steven F. Bolling, a cardiac surgeon at the University of Michigan Cardiovascular Center, who also heads the Cardioprotection Research Laboratory at the University of Michigan, had the lead quote in a news story about these findings:

"We've always known fruits and vegetables were "healthy," but now we're beginning to better understand precisely why...Researchers are uncovering the unique potential for plant compounds, like those in cherries, to affect multiple heart health factors. For cherries, we're learning the benefits may come from effects on both cholesterol levels and inflammation."

Sounds like good news for people seeking foods that promote health. A recent survey revealed most respondents would prefer to eat or drink foods with health-promoting properties, with heart health topping the list, if they knew it could potentially limit the amount of medication they needed to take.

Research on Phytochemicals to Prevent Cancer Is Booming

An editorial last year in Seminars in Cancer Biology noted that a recent search of PubMed turned up hundreds of publications on phytochemicals and prevention of cancer. In its opening sentence, the editorial stated that "the importance of cancer prevention continues to grow due to..."
poor prognosis of advanced cancers, inadequate therapeutic responses, and toxicities associated with chemo- and radio-therapies." Other factors in the growth of scientific literature on phytonutrients, according to the editorial, included the limited success of educational programs in reducing tobacco use and exposure to environmental and workplace carcinogens.

Consequently, the National Institutes of Health (NIH) and other health organizations have been turning more and more to setting dietary guidelines for cancer prevention and funding studies on how dietary supplements could affect the initiation and progression of cancer. Lately, these studies have concentrated on protective effects believed to come from the high levels and variety of phytonutrients in dark-colored fruits and vegetables.

Following the prevailing theory of carcinogenesis, the editorial explained:

Carcinogenesis is a multifaceted process involving initiation, promotion, and progression...Opportunities exist for intervention at each of these stages by phytonutrients. Since tumor initiation typically involves irreversible genetic damage, prevention of initiation by phytonutrients may involve (i) inactivation of the carcinogen, (ii) inhibition of phase I carcinogen activating enzymes, and/or (iii) induction of phase II detoxifying enzymes. Thus, phytonutrients may have multifunctional mechanisms and molecular targets in cancer prevention.

The rest of the editorial specifies some of the mechanisms and molecular targets. The last paragraph ambitiously and optimistically projects the goals of phytonutrient research:

"The future is ripe for identifying fruits and vegetables and individual phytonutrients with cancer-preventing activity. As we identify the molecular mechanisms and target by which individual phytonutrients prevent cancer, we may be able to improve upon nature by formulating phytonutrient cocktails for specific cancers and individual susceptibility and risk" (emphasis added).

Implicit in improving on nature is the expectation that the cocktail formulas will be patentable, developed by drug companies for colossal profits, perhaps available only by prescription if the FDA classifies them as "new drugs" that require pre-marketing testing, and outrageously more expensive than buying the fruits and vegetables at the produce market - and maybe not an improvement at all, if the phytonutrients are served up as isolates from the whole fruit or vegetable.

Whole Berries in Cancer Prevention

A paper appearing in the Journal of Agricultural and Food Chemistry in February 2008, reviewed recently published studies of whole berries. Under the term "whole berries," the author included single and combined berry formulations, berry extracts, freeze-dried powders, purified fractions, and beverages. The paper focused on berries commonly eaten in North America: blackberries, black raspberries, red raspberries, cranberries, blueberries, and strawberries.

Berries, the author said, make up the largest percentage among small, soft-fleshed, colorful fruits in the North American diet. "Overwhelming evidence suggests that...berry fruits may have beneficial effects against several types of human cancers." That anticancer potential, according to the author (referring to a growing body of studies), relates to numerous berry phytochemicals whose bioactivity is diverse.

Berry phytochemicals can reduce or repair damage from inflammation and oxidative stress. They can regulate subcellular signaling pathways involved in angiogenesis, cancer proliferation, and apoptosis. (Angiogenesis is the formation and differentiation of blood vessels. Apoptosis is the genetically determined process of cell self-destruction.) Berry phytochemicals may sensitize tumor cells to chemotherapy by inhibiting pathways that help tumors resist treatment. Just eating berries may protect against the toxic effects of chemotherapy and radiation.

As this is a scientific paper, the language is fittingly technical, making it a slow and tough read, but the coverage is comprehensive. Berry phytochemicals are specified, and their potential mechanisms of action, bioavailability, and dietary intake are discussed briefly. Anticancer studies are sectioned off into research in the laboratory (in vitro), tests in animals, and evaluation in humans.

In the "Summary and Future Perspectives" section, the author makes suggestions for further research, three of which merit quoting:

Whether the chemopreventive potential of berry bioactives is increased by complex interactions of multiple substances within the natural food matrix of berry fruits, and/or in combination with phytochemicals from other foods, should be investigated.

In addition, studies probing potential "herb-drug" interactions of berries and pharmaceutical drugs should be investigated in carefully planned and controlled human clinical studies.

Finally, interdisciplinary research is highly recommended so that basic and preclinical studies can lead to translational research (from laboratory to bedside).

"OptiBerry" Smoothies?

Hopefully, "translational research" on berries won't extend a decade or more before general application. Meanwhile, people keen on avoiding cancer might try a combination of extracts from bilberries, blueberries, cranberries, elderberries, raspberry seeds, and strawberries. A research article published in 2007 evaluated this particular selection of berry extracts, finding that it acted synergistically to produce safer and stronger effects compared with the berries individually and with other combinations of berry extracts.9 "OptiBerry," as the researchers called it, also showed superior bioavailability.

All these berries contain anthocyanins, phytochemicals that color fruit blue, purple, or red. In recent studies, berry anthocyanins were mainly responsible for the high
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antioxidant activity demonstrated, according to the investigators. The investigators also found evidence in the studies that berry anthocyanins have the potential to inhibit cancers of the colon, esophagus, liver, and oral cavity through several mechanisms of action.

Tested against *Helicobacter pylori*, a bacterium estimated to infect half the population of the world, "OptiBerry" demonstrated bactericidal activity. A causative factor in many gastrointestinal diseases, including duodenal ulcer and gastric cancer, *H. pylori* is growing resistant to the antibiotic of choice against it, clarithromycin, so this finding offers a natural treatment for it.

Tested in hamsters for atherosclerosis, "OptiBerry" dramatically ameliorated its incidence. The researchers thought that the protective effect in this cardiovascular condition is due partly to the antioxidant properties of anthocyanins. Other tests of the berries separately indicated that anthocyanins in bilberries, blueberries, and strawberries helped preserve brain and neurological functions that aging often impairs.

Other findings that rate mention include the following: bilberries, used in Europe for centuries to moderate diabetes, were shown to normalize diabetic hyperglycemia in rats. Bilberry and other berry anthocyanins can improve night vision by enhanced generation of retinal pigments. In addition, these berry phytochemicals appear to increase circulation in capillaries in the retina, decrease diabetic retinopathy and macular degeneration, and improve or prevent cataracts, glaucoma, and *retinitis pigmentosa*. In connection with berries and vision, the authors of the 2007 research paper noted that British Air Force pilots loaded up on bilberry jam before bombing missions during World Wars I and II; the jam seems to have sharpened their eyesight, particularly on night runs.

Grape Phytochemicals Inhibit Key Enzyme in Cancer

Phytochemical constituents of dark-colored grapes work synergistically to inhibit an enzyme central to proliferation of cancer cells. Two studies published in *The Journal of Agricultural and Food Chemistry* in 2005 and 2006 provide the basis for this scientific finding. Utilizing advanced molecular technology, the research team that conducted these studies evaluated possible inhibitory effects of grape cell culture extract and subfractions on human DNA topoisomerase II catalytic activity. Both studies, it should be noted, were supported by the National Center for Complementary and Alternative Medicine (NCCAM), established in the National Institutes of Health in 1997.

Topoisomerases are essential enzymes in cell proliferation in all organisms. They are involved in recombination, replication, transcription, and translation of DNA, and in chromosome dynamics. Topoisomerase II is vital in cell division and cell proliferation; mitosis cannot be completed without it. Highly proliferative tumor cells often express 25-300 times higher levels of this enzyme than those of differentiated (normal) cells.

A diverse group of chemotherapeutic agents for cancer has been developed to target topoisomerase II. These inhibit the proliferative action of tumor cells. Of course, they have undesirable toxic side effects. The worldwide consumption of grapes offers an opportunity to investigate their phytochemical constituents as a "natural" means of preventing cancer.

Grape cell culture extracts are rich in flavonoids, among other phytochemicals. These studies showed that two classes of the varied flavonoid family, proanthocyanidins and anthocyanins, are mainly responsible for the synergistic activity. More importantly, they revealed that the fractions of grape cell culture extract powerfully inhibit the topoisomerase II enzyme through a mechanism independent of antioxidant capacity.

Most importantly, the studies found that the antitopoisomerase II catalytic activity of TP-4 and TP-6, the two most potent fractions, was significantly greater than activity previously reported for recognized chemopreventive agents such as ellagic acid, genistein, quercetin, and resveratrol.

In a project funded by the US Department of Agriculture, the researchers have since begun tracing where radio-labeled flavonoids from whole grapes congregate in rats. The ultimate aim of all their studies is to determine reasonable dosages for the therapeutic consumption of flavonoid-rich grapes.

Compounds that Color Fruits and Vegetables May Protect Against Colon Cancer

Experiments on rats and on human cancer cells suggest that anthocyanins appreciably slow the growth of colon cancer cells. These findings were presented at the national meeting of the American Chemical Society in Boston August 19th, 2007. Fruits and vegetables with intensely deep color were selected for the experiments because they are the richest in anthocyanins. Common and exotic fruits and vegetables were in the mix, including bilberries, chokeberries, elderberries, grapes, purple carrots, and purple corn. Some of these plants are commercially used as food colorings.
Whether in laboratory dishes or inside the human body, all edible plants high in anthocyanins, the investigators suggested, may inhibit the growth of colon cancer cells. They also suggested that anthocyanins might protect against several other forms of gastrointestinal cancer. The probable reason, according to the researchers is that the bloodstream absorbs little anthocyanin. A large proportion travels through the gastrointestinal tract, where these tissues do absorb this phytochemical.

In additional experiments, the researchers discovered that anthocyanin pigments from black carrots and radishes slowed the growth of cancer cells anywhere from 50% to 80%. Pigments from chokeberries and purple corn not only completely stopped cancer cell growth, they also killed roughly 20% of the cancer cells while having little adverse effect on normal cells.

Studies on rats induced with colon cancer cells demonstrated similar beneficial results. Fed a daily diet of anthocyanin extracts from either bilberries or blackberries, these animals had signs of cancer reduced by 70% and 60%, respectively, compared to control rats. There was scarcely any effect on normal cells. (Extracts from bilberries and blackberries have proven safe in commercial use as flavorings or to make jams and juices.)

The foods tested contain many compounds, said the researchers. Scientists are only beginning to identify them and piece out which ones offer the best health benefits. There are 600 different anthocyanins, and investigation has merely scratched the surface of grasping how the body absorbs and uses these different structures.

Pectin Causes Prostate Cancer Cells to Commit "Suicide"

Normal cells mature to perform the functions nature intended them to perform in the organ or the place in the body to which they belong. This process is known as differentiation. Cancer cells don't grow up but keep proliferating, behaving as though they are immortal.

Some conventional chemotherapy and anti-hormone treatments for certain cancers are designed to induce apoptosis. Prostate cancer — in men, the commonest malignancy and the second-leading cause of death — creates a treatment challenge, because there are prostate cancer cells for which androgen deprivation therapy can induce apoptosis and androgen-insensitive cells that remain unaffected. (Androgens are male sex hormones, and androgen deprivation treatment is referred to casually as "chemical castration.") But androgen-insensitive prostate cancer cells are capable of undergoing apoptosis, so the discovery of novel means to get prostate cancer cells to commit "suicide," regardless of their response to hormones, is a busy avenue of research.

Enter pectin, a polysaccharide constituting roughly 30% of primary cell walls in higher plants — and thus a dietary component of all fruits and vegetables. A study published in Glycobiology in 2007 demonstrated that pectin induces apoptosis in hormone-responsive and hormone-independent prostate cancer cells.12 Their study, claim the authors, is the "first extensive analysis correlating structural features of pectin with apoptosis-inducing activity in cancer cells."

Summarizing previous findings on pectin and cancer by other researchers, the authors referred to reports dating from 1992 that pectin has indicated anti-carcinogenic activity in colon, lung, myeloma, skin (melanoma), and even prostate cancers. (Oral administration of pH-modified citrus pectin reduced metastatic prostate cancer in rats.) They thought it "noteworthy that those anti-metastatic effects of pectin occurred in the absence of cell toxicity." Let's highlight those effects in late-stage cancer: unlike chemotherapy,
pectin is non-toxic. The authors, in an aside of sorts, added that pectin has been shown to lower cholesterol and glucose levels in humans.

According to the authors, pectin is a very complex molecule, potentially able to bind to several cell sites and produce several different cellular responses at the same time. The investigators analyzed three different types of commercially available pectin, observing significant differences in anti-cancer activity. Heat treatment increased the activity. Exposing prostate cancer cells to pectin under laboratory conditions reduced the number of cells by as much as 40%.

In conclusion, the authors called for more studies to support use of specific pectin supplements, advising Americans simply to eat lots of fruits and vegetables, which by itself would supply lots of pectin and provide other naturally occurring beneficial phytochemicals. "An apple a day keeps the doctor away" – there lots of pectin in an apple. Old wives' tale, folk wisdom, or empirical acceptance, there's now some science behind the adage.

Same Old, Same Old...

By citing studies published between 2005 and 2008, this column may have created the impression that research on phytochemicals and cancer prevention is a relatively late development. But the peer-reviewed literature on diet and disease in general extends back more than half a century. Herbert F. Pierson, PhD, published one paper that is especially pertinent to phytochemicals in 1993.13 In the early 1990s, Dr. Pierson headed the phytochemical division of the Chemoprevention section in the National Cancer Institute (NCI). His division specialized in "Designer Foods" – a term spawned within the NCI oriented toward research on the connections between phytochemical constituents in foods and dietary supplements and cancer prevention.

The following paragraph from that paper describes one of four approaches to designer food development:

One approach...involves the evaluation of human gastrointestinal absorption of food phytochemicals (physiological approach). Citrus is used as a model for this approach in that citrus is a rich source of antioxidants, antimutagens, anticarcinogens, and chemoprotective compounds. The first step is to chemically fingerprint the major classes of total citrus phytochemicals in pure orange juice (free plus bound phytochemicals). After determining the concentration of the top twenty antioxidative and antimutagenic citrus phytochemicals in pure orange juice, the standardized juice (where eight ounces represents equivalence to four oranges) is fed to healthy humans who are subsequently evaluated for the presence of the twenty phytochemicals in their blood sera. Analysis reveals that eight out of twenty citrus phytochemicals are absorbed and measurable in sera. Next, a redesigned orange juice is made by fractioning and concentrating the eight absorbable citrus phytochemicals in pure orange juice so that eight ounces represents the equivalence of perhaps twenty oranges. There is no legal restriction on anyone consuming twenty oranges daily, but if you construct a juice beverage where twenty orange equivalents of absorbable phytochemicals are present in an eight-ounce serving, it could be considered by the FDA to be a drug. It will certainly be considered a drug if the natural phytochemical enrichment with flavonoids is designed to chelate and help eliminate lead from the bodies of school children or inhibit aldol reductase, the cataract-causing enzyme in the eyes of diabetics.

Uh, oh! What would the FDA do if the scientists who reported on "OptiBerry" interested a food company in marketing the blend and the company slapped a label on the bottle saying there is scientific evidence that "Optiberry" prevents cancer, kills H. pylori, works against cardiovascular disease, etc.?

A rational plan to cover uninsured Americans while slashing the cost of health care might include ways to increase consumption of the sort of phytochemicals discussed in this column – ways not limited to the uninsured. With a presidential election upcoming this fall, and the front-running Democratic contenders offering competing plans for universal health coverage, the next column will propose several means and routes around obstacles to the realization of such proposals.

Notes
5. Survey of 1,507 adults age 45 and older by the Caravan Services, Opinion Research Corporation, November 2007, on behalf of the Cherry Marketing Institute.
8. Ibid.
12. EurekAlert.org; 8/19/07.