

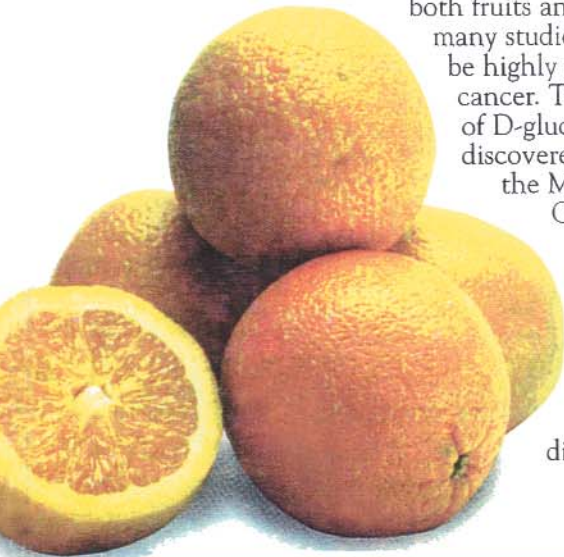
THE GLUCARATE REPORT

D-Glucarate Helps Remove Toxins and Carcinogens From the Body

Cancers develop gradually as a result of a complex interaction of factors related to heredity, environment, lifestyle and diet (NAS, 1982; Slaga, 1980 a and b). Based on sound scientific estimates, it can be stated that greater than 80 percent of all cancer deaths are related to the use of tobacco products, to what we eat and drink, to exposure to sunlight and ionizing radiation and to exposure to cancer-causing chemicals found in the environment and the workplace (Doll and Peto, 1981). No doubt, some people are more sensitive than others to factors that cause cancer; however, personally controlled lifestyle factors account for the major cancer risk experienced by mankind.

More than 200 epidemiological studies show that a diet high in fruits and vegetables leads to a decrease in cancer as well as other degenerative diseases (Steinmetz and Potter, 1991 a and b). In addition, thousands of human and experimental animal studies show the protective effects of vitamins, minerals, antioxidants and other beneficial phytochemicals against cancer and other degenerative diseases.

D-glucarate is a nontoxic, natural substance found in both fruits and vegetables, and many studies have shown it to be highly protective against cancer. The health benefits of D-glucarate were discovered by researchers at the M.D. Anderson Cancer Center, the No. 2 cancer center in the United States. They have developed a patented form of glucarate for use in dietary supplements.



In experimental animal studies, D-glucarate has been shown to decrease lung, skin, liver, breast and colon cancers by 60 percent or more (Walaszek, 1990). In addition, D-glucarate has been found to have an inhibitor effect on cancers of the bladder and the prostate.

In the breast, D-glucarate has been shown in more than 20 experimental animal and *in vitro* studies to significantly inhibit cancer. D-glucarate inhibits the induction of breast cancer by a variety of chemical carcinogens and tumor promoters including estrogens. D-glucarate has been found to work synergistically with both retinoids and tamoxifen to prevent the induction of breast cancer. The primary mechanism of action of D-glucarate is through its ability to enhance detoxification of both chemical carcinogens from the environment and estrogenic tumor promoters produced by the body. Women who are at a higher risk for breast cancer have a lower detoxification capacity for carcinogens and estrogens. Several human trials are currently underway with D-glucarate to determine its capability to decrease the breast cancer risk in women at a high risk for breast cancer.

Likewise, D-glucarate has been found to effectively prevent the induction of prostate cancer in men. An enhancement of the detoxification of carcinogens and androgens appears to be the mechanism by which D-glucarate inhibits prostate cancer. Several experimental animal studies have likewise shown the protective effect of calcium D-glucarate against colon cancer induced by various potent carcinogens. Once again, the mechanism by which calcium D-glucarate inhibits colon cancer appears to be related to the enhancement of the detoxification of both carcinogens and sterol tumor promoters.

In studies of lung cancer, a leading cause of death in this country, D-glucarate has been shown to effectively inhibit the induction of this form of cancer in experimental animal studies using different types of carcinogens found in cigarette smoke. Detoxification of these carcinogens appears to be the major mechanism of action.

CONTINUED FROM COVER

D-glucarate also appears to have beneficial applications with cancers of the liver, bladder and skin; although, more research is needed. In all reviewed cases, the mechanism of action of D-glucarate appears, once again, to be related to the enhanced detoxification and inhibition of cell proliferation.

Of particular importance, the protective effect observed in experimental animal studies of D-glucarate and its derivatives against cancers of the breast, prostate, colon, lung, liver, bladder and skin appears associated with a considerable inhibition of both the initiation and promotion stages of carcinogenesis. Similar amounts of a calcium control — calcium gluconate — did not provide protection. In a review of all studies performed to date, D-glucarate and its derivatives appear promising as chemopreventive agents against several different cancers.

The mechanism by which D-glucarate enhances the detoxification of carcinogens, steroids and sterols seems to be associated with its ability to inhibit the enzyme β -glucuronidase. The major mechanism by which carcinogens, steroid hormones and sterols are detoxified is through a process called conjugation by glucuronidation. β -glucuronidase effectively reverses this reaction allowing active carcinogens and tumor promoters to do further damage.

It is important to note that D-glucarate is a natural compound produced in small amounts by mammals, including humans, and by some plants. Studies of D-glucarate and its derivatives reveal no toxicity when consumed in large amounts, making it a safe substance to ingest. If glucarate were not produced in small amounts by the human body, it would more than likely be classified as a vitamin because of its beneficial role in protecting against cancer. Dietary sources of D-glucarate include different fruits and vegetables. The highest amounts of D-glucarate are found in fruits, especially apples, grapefruits, cherries and apricots. Significant amounts are also found in vegetables including broccoli, brussel sprouts and alfalfa sprouts. ■

An Interview With Dr. Thomas Slaga

Dr. Thomas Slaga is the Executive Vice President for Research and the Chair of the Center for Cancer Causation and Prevention at the AMC Cancer Research Center in Denver, Colo. He oversees the development of research programs that focus on major cancer target sites, including the breast, colon, prostate gland and skin. He also directs activities in other areas of cancer study including molecular epidemiology, genetic monitoring and cancer interventions. Recently, we sat down with Dr. Slaga to gather his insights on calcium D-glucarate.

What is calcium D-glucarate?

Dr. Slaga: Calcium D-glucarate is a patented form of glucaric acid. Glucaric acid is already present in small amounts in our bodies and is found in certain fruits and vegetables. It enhances the process known as glucuronidation, a process by which the body rids itself of potentially dangerous carcinogens and other harmful chemicals. Calcium D-glucarate is a form of glucaric acid, which is effectively utilized in the body. D-glucarate is a unique, nontoxic and natural substance found in both fruits and vegetables. Many studies have shown this substance to be highly protective against cancer.

If glucaric acid is produced in our bodies and occurs naturally in fruits and vegetables, why would one take calcium D-glucarate supplements?

Dr. Slaga: Research indicates that taking calcium D-glucarate is beneficial. The substance enhances the body's natural enzymatic process of detoxification. Taking glucarate appears to increase detoxification of harmful chemicals, and this helps to prevent disease. Additional amounts of glucarate are especially important for individuals who are exposed to more harmful chemicals, such as cigarette smoke and individuals who have a high risk for certain cancers, like breast, lung and prostate cancer. The typical American diet does not include enough fruits and vegetables to maintain an effective level of glucarate; therefore, additional amounts can only help the body fight the harmful chemicals.

I recommend that individuals eat a healthy diet such as five servings of fruits and vegetables per day plus take calcium D-glucarate supplementation in order to get sufficient protection against carcinogens and toxic agents.

Glucuronidation



1. Glucarate enters cells.



2. Carcinogens attack cells.



3. Through glucuronidation, harmful substances are removed from cells, made water soluble and eliminated from body.



4. A harmful enzyme often glucuronidation, releasing back into the body.



5. Glucarate from cells bonds with the enzyme, preventing its harmful action.

It has been stated that calcium D-glucarate helps prevent cancer. Is this true? If so, how does it do that?

Dr. Slaga: As I mentioned before, calcium D-glucarate is a substance that aids in glucuronidation, which is one of the body's major detoxification systems for eliminating both foreign chemicals and endogenous chemicals, such as steroids and sterols. Glucuronidation is a reaction where a toxin is made water-soluble so that it can be more easily excreted in the urine or the bile. Calcium D-glucarate inhibits an enzyme, present in many tissues of the body and in the microflora of the intestines, which reverses detoxification. Calcium D-glucarate inhibits the detoxification-reversing enzyme β -glucuronidase.

If you will, calcium D-glucarate inhibits the "bad enzyme" in the detoxification process.

In a general sense, calcium D-glucarate helps the body's process for eliminating harmful toxins and carcinogens that occur naturally or come from things like tobacco smoke, pesticides and other foreign substances. In addition, calcium D-glucarate helps eliminate excess amounts of chemicals produced in the body that promote cancer, such as estrogens and androgens. With more of these substances eliminated, an individual may rid his or her body of some of the things that lead to cancer. So, yes, it may be a promising tool against cancer.



reverses carcinogens

How exactly does calcium D-glucarate help with the glucuronidation process?

Dr. Slaga: As we discussed, the body gets rid of harmful substances by making them more water soluble and more excretable. In individuals at risk for cancer, glucuric acid levels are low and are excreted quickly from the body. With low levels of the inhibitor glucuric acid, β -glucuronidase activity is high and there is less

excretion of carcinogens and toxins. If an individual were to have higher levels of glucuric acid, he or she may be able to slow down the work of the "bad enzyme," β -glucuronidase, and rid his or her body of dangerous toxins and carcinogens. Calcium D-glucarate first associates into calcium and glucuric acid in the body, and then glucuric acid spontaneously converts to a lactone that inhibits the bad enzyme.

What are the research findings about calcium D-glucarate and its role against cancer?

Dr. Slaga: In experimental animal studies, D-glucarate has been shown to decrease lung, skin, liver, breast and colon cancers by 60 percent or more. In addition, D-glucarate has been found to have an inhibitor effect on cancers of the bladder and the prostate.

In the breast, D-glucarate has been shown in more than 20 experimental animal and *in vitro* studies to significantly inhibit cancer. Several human trials are currently underway with D-glucarate to determine its capability to decrease the breast cancer risk in women at a high risk for breast cancer.

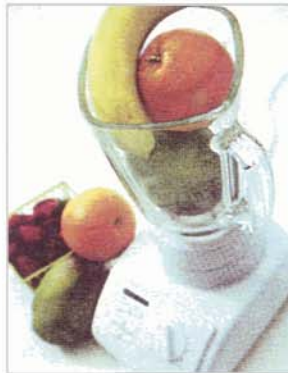
GLUCARATE ... IN BRIEF

- Glucarate is a component of fruits and vegetables and is present in the human body.
- Glucarate is safe; no toxicity has been detected.
- Glucarate is a pure compound that's molecular structure and mechanism of action is well defined.
- Glucarate supports the major detoxification pathway in the body: glucuronidation. This is the body's primary defense against cancer-causing agents.
- Shown to inhibit the development of cancers in laboratory animals in more than 30 studies published in cancer research journals.
- Glucarate in lab animals has been shown to be effective in preventing breast, lung, prostate, skin, colon, bladder and liver cancers.
- Clinical trials are underway by the National Cancer Institute and the AMC Cancer Research Center on glucarate as a cancer-preventative agent.
- Epidemiological evidence shows a positive correlation between higher glucarate levels and reduced cancer risk.
- Researchers at M.D. Anderson Cancer Center, the No. 2 cancer center in the United States, developed a patented form of glucarate used in dietary supplements.
- Recommended daily supplement dosage is 200 to 400 mg.

CONTINUED FROM INSIDE

In addition, several experimental animal studies have shown the protective effect of calcium D-glucarate against colon cancer. Once again, the mechanism by which calcium D-glucarate inhibits colon cancer appears to be related to the enhancement of the detoxification of both carcinogens and sterol tumor promoters.

In studies of lung cancer, a leading cause of death in this country, D-glucarate has been shown to effectively inhibit the induction of this form of cancer in experimental animals using different types of carcinogens found in cigarette smoke. Currently there are ongoing studies of the effect of calcium D-glucarate on individuals determined to be at high risk for the development of lung cancer.



At this time, limited data in experimental animal models are available on the effect of D-glucarate on cancers of the liver, the bladder and the skin. However, there appears to be beneficial application.

Why is calcium D-glucarate being targeted to people at risk for breast cancer?

Dr. Slaga: Research suggests that women at risk for the development of breast cancer may excrete estrogen less effectively than women at lesser risk. The same reactions that promote the excretion of carcinogens promote the excretion of estrogen metabolites.

R E F E R E N C E S

- Slaga, T.J. Modifiers of chemical carcinogenesis: an approach to biochemical mechanism and cancer prevention. Raven Press, N.Y., 1980(a).
- Slaga, T.J. Food additives and contaminants as modifying factors in cancer induction. Nutrition and Cancer, Raven Press, 1980; 279-90(b).
- Doll R., Peto R. The cause of cancer. Quantitative estimates of available risks of cancer in the United States today. J Natl Canc Inst, 1981;66: 1192-1308.
- Steinmetz K., Potter J.D. A review of vegetables, fruit and cancer. Epidemiology, cancer causes and control. 1991;2:325-57.
- Alexandra S. Heerd, Charles W. Young and Patrick I. Borgen. Calcium glucarate as a chemopreventive agent in breast cancer. 1st J Med Sci. 1995;31:101-105.
- Zbigniew Walaszek. Potential use of D-glucaric acid derivatives in cancer prevention. Cancer Letters, 54 (1990) 1-8 Elsevier Scientific Publishers Ireland Ltd.
- H. Abou-Issa, M. Moeschberger, W. Ei-Masry, S. Tejwani, R.W. Curley, Jr. and T.E. Webb. Departments of Surgery, Preventive Medicine and Medical Biochemistry and Medicinal Chemistry, Colleges of Medicine and Pharmacy, Ohio State. Relative efficacy of glucarate on the initiation and promotion phases of rat mammary carcinogenesis. Anticancer Research 15:805-810 (1995).
- Zbigniew Walaszek, Ph.D., Janusz Szemraj, Ph.D., Maciej Narog, M.D., Alan K. Adams, B.S., James Kilgore, B.S., Ute Sherman, M.S., and Malgorzata Hanausek, Ph.D. Metabolism, uptake and excretion of a D-glucaric acid salt and its potential use in cancer prevention. Cancer Detection and Prevention 21(2):178-190 (1997).
- Elizabeth Kyle, M.S., Annette Carpet, M.S., and Phyllis Bowen, Ph.D. Caffeine consumption and vegetarian diets affect D-glucarate acid excretion in man. Nutrition Research, Vol. 7, pp. 461-470, 1987 0271-5317/87.
- Zbigniew Walaszek, M. Hanausek, U. Sherman and A.K. Adam. Antiproliferative effect of dietary glucarate on the Sprague-Dawley rat mammary gland. Cancer Letters, 49 (1990) 51-57 Elsevier Scientific Publishers Ireland Ltd.
- O.A. Oredipe, R.F. Barth, C. Dwivedi and T.E. Webb. Dietary glucarate-mediated inhibition of initiation of diethylnitrosamine-induced hepatocarcinogenesis. Departments of Pathology and Medical Biochemistry, The Ohio State University and College of Pharmacy, South Dakota State University. Toxicology, 74 (1992) 209-222 Elsevier Scientific Publishers Ireland Ltd.
- Waguihel-Masry and Thomas E. Webb. Departments of Surgery, Internal Medicine and Medical Biochemistry, College of Medicine and College of Pharmacy, The Ohio State University; College of Pharmacy, South Dakota State University. Basis for the anti-tumor and chemopreventive activities of glucarate and the glucarate:retinoid combination. Anticancer Research 13: 395-400 (1993).
- Thomas E. Webb, Hussein Abou-Issa, Paul C. Stromberg, Robert C. Curley Jr. and Mai-Houng Pham Nguyen. Departments of Medical Biochemistry and Surgery, College of Medicine and Pathobiology, The College of Veterinary Medicine and College of Pharmacy, The Ohio State University. Mechanism of growth inhibition of mammary carcinomas by glucarate and the glucarate: retinoid combination. Anticancer Research 13: 2095-2100 (1993).
- Oladipo A. Oredipe, Rolf F. Barth, Malgorzata Hanausek-Walaszek, Iveta Sautins, Zbigniew Walaszek and Thomas E. Webb. Effects of calcium glucarate on the promotion of diethylnitrosamine-initiated altered hepatic foci in rats. Departments of Pathology and Physiological Chemistry, The Ohio State University. Cancer Letters, 38 (1987) 95-99 Elsevier Scientific Publishers Ireland Ltd.
- Hussein M. Abou-Issa, Valentine A. Duruibe, John P. Minton, Saroj Larroya, Chandradhar Dwivedi and Thomas E. Webb. Putative metabolites derived from dietary combinations of calcium glucarate and N-(4-hydroxyphenyl) retinamide act synergistically to inhibit the induction of rat mammary tumors by 7, 12 dimethylbenz[*a*]anthracene. Comprehensive Cancer Center and the Departments of Surgery and Physiological Chemistry, The Ohio State University. Proc. Natl. Acad. Sci. USA Vol. 35, pp. 4181-4184, June 1988 Biochemistry.
- Chandradhar Dwivedi, Wendy J. Heck, Alan A. Downie, Saroj Larroya, Thomas E. Webb. College of Pharmacy, South Dakota University and Department of Physiological Chemistry, College of Medicine and the Comprehensive Cancer Center, The Ohio State University. The effect of calcium glucarate on β -glucuronidase activity and glucarate content of certain vegetables and fruits. Biochemical Medicine and Metabolic Biology 43, 83-92 (1990).
- Thomas E. Webb, Mai-Houng Pham-Nguyen, Michael Darby's and Ashton T. Hamme, Department of Medical Biochemistry, College of Medicine and The Comprehensive Cancer Center, The Ohio State University. Pharmacokinetics relevant to the anticarcinogenic and anti-tumor activities of glucarate and the synergistic combination of glucarate:retinoid in the rat. Department of Medical Biochemistry, College of Medicine and the Comprehensive Cancer Center, The Ohio State University. Corresponding author: Thomas E. Webb, Ph.D., Department of Medical Biochemistry, The Ohio State University College of Medicine. Biochemical Pharmacology, Vol. 47, No. 9, pp. 1655-1660, 1994.
- Marios Marselos, Geoffrey Dutton and Osmo Hänninen. Evidence that D-Glucaro-1,4-lactone shortens the pharmacological action of drugs being disposed via the bile as glucuronides. Biochemical Pharmacology, Vol. 24, pp. 1855-1858.
- O. Sandstad, T. Osnes, V. Skar & M. Osnes. Urinary D-glucaric acid, a marker substance for microsomal enzyme induction. Methodological aspects, responses to alcohol and findings in workers exposed to toluene. Scand J Clin Lab Invest 1993; 53:327-333.
- M. Lohmeyer, L. McNaughton, S.P. Hunt and P. Workman. Stimulation of intracellular free calcium increases by platelet-activating factor in HT29 colon carcinoma cells. MRC Units of Clinical Oncology and Radiotherapeutics and Molecular Neurobiology, MRC Centre, U.K.; and CRC Department of Medical Oncology, CRC Beatson Laboratories, Glasgow University, U.K. MRC Division of Development Neurobiology, MRC National Institute for Medical Research, U.K. ZENECA Pharmaceuticals, Cancer Research Dept., U.K. Biochemical Pharmacology, Vol. 47, No. 6. pp. 975-985, 1994.