

Cancer Prevention
Updated: 08/26/2004

ABSTRACTS

Chlorophyllin as a protector of mitochondrial membranes against gamma-radiation and photosensitization.

Bolloor KK, Kamat JP, Devasagayam TP.

Toxicology. 2000 Nov 30; 155(1-3):63-71.

Ionizing radiation and photosensitization are highly damaging events and they generate oxygen-derived free radicals as well as excited species. However, the types as well as extent of reactive oxygen species (ROS) differ. They have been linked to various pathological conditions. Hence natural compounds capable of preventing oxidative damage induced by these agents may have potential applications. Chlorophyllin (CHL), the water-soluble analogue of chlorophyll, has been examined for its ability to inhibit membrane damage induced by γ -radiation and photosensitization involving methylene blue plus visible light. Using rat liver mitochondria as model systems the mechanisms of damage induced by these two agents as well as its possible prevention by CHL have been examined. The parameters used were lipid peroxidation as assessed by formation of thiobarbituric acid reactive substances (TBARS) and 4-hydroxynonenal (4-HNE), protein oxidation besides glutathione (GSH) and superoxide dismutase (SOD). Peroxidation increases with radiation dose, in the range of 75-600 Gy. A similar observation also was observed with photosensitization, as a function of time. CHL, at a concentration of 10 microM offered a high degree of protection against radiation and photosensitization as indicated by decreased peroxidation, protein oxidation as well as the restoration of GSH and SOD. When compared with the established antioxidants, ascorbic acid and GSH, CHL offered a much higher degree of protection. Pulse radiolysis studies show that this compound has a relatively high rate constant with hydroxyl radical (*OH), a crucial species generated during γ -radiation. Hence the studies show that CHL is a potent antioxidant in mitochondrial membranes

Chlorophyllin chemoprevention in trout initiated by aflatoxin B(1) bath treatment: An evaluation of reduced bioavailability vs. target organ protective mechanisms.

Breinholt V, Arbogast D, Loveland P, et al.

Toxicol Appl Pharmacol. 1999 Jul 15; 158(2):141-51.

Chlorophyllin (CHL) is known to inhibit DNA adduction and hepatocarcinogenesis in trout when administered at doses up to 4000 ppm in the diet with aflatoxin B(1) (AFB(1)). The principal protective mechanism is believed to involve CHL:AFB(1) complex formation, which may reduce systemic carcinogen absorption. However, mechanisms operative within the target organ in situ have not been ruled out. The present study used alternative CHL and AFB(1) exposures as well as hepatic metabolism studies to distinguish these mechanisms. Duplicate lots of 150 rainbow trout each were initiated by brief water bath exposure to 0.1 ppm AFB(1), with or without 500 ppm CHL in the water. The addition of 500 ppm CHL to the water bath, under conditions where AFB(1) is calculated to be >99% sequestered as the CHL:AFB(1) complex, reduced hepatic AFB(1)-DNA adduction by 95% and reduced hepatocarcinogenesis from 20.5% to 2%, compared with exposure to AFB(1) alone. Inclusion of 500 ppm CHL in the water bath also significantly reduced total body burden and hepatic levels of AFB(1) as well as AFB(2), a structural analogue of AFB(1) unable to directly form the 8,9-epoxide proximate electrophile but equally capable of complexing with CHL. By contrast, internal target organ CHL loading by pretreatment of trout with 4000 ppm dietary CHL for 7 days prior to (and 2 days following) AFB(1) waterbath exposure had no effect on AFB(1)-DNA adduction or tumorigenicity. Dietary CHL up to 8000 ppm had no effect on hepatic CYP2K1, CYP1A, glutathione transferase, UDP-glucuronosyl transferase, or, with one exception, the relative ratios among hepatic AFB(1) metabolites in vivo. These results support the hypothesis that CHL:AFB(1) complex formation and reduced systemic AFB(1) bioavailability is a principal mechanism for CHL chemoprevention in this model and that in situ target organ inhibitory mechanisms are relatively insignificant

Effect of five dietary antimutagens on the genotoxicity of six mutagens in the microscreen prophage-induction assay.

Cabrera G.

Environ Mol Mutagen. 2000; 36(3):206-20.

Dietary antimutagens have been studied extensively in the last two decades, using mainly bacterial and mammalian cells. These studies have shown that certain dietary antimutagens, acting individually or as mixtures, are useful in counteracting the effects of certain mutagens and/or carcinogens to which humans are commonly exposed. However, there are some inconsistencies among publications using different bioassays. The general purpose of the research presented here was to conduct a comparative study of the antigenotoxic activity of five dietary antimutagens against six mutagens, using three rather different short-term tests: the Microscreen prophage-induction assay, the Tradescantia micronucleus test, and the Salmonella/mammalian microsome test. In this study I report the results with the Microscreen prophage-induction assay. The antimutagens selected were chlorophyllin, beta-carotene, and vitamins A, C, and E. The mutagens selected were 2-aminoanthracene, benzo[a]pyrene, 2-nitrofluorene, toxaphene, dichlorvos, and nitrofen. The results show that chlorophyllin and beta-carotene inhibited the genotoxicity of all six mutagens; vitamin E inhibited all except dichlorvos; and vitamins C and A inhibited 2-aminoanthracene, benzo[a]pyrene, 2-nitrofluorene, and nitrofen

Protective effects of hemin and tetrakis(4-benzoic acid)porphyrin on bacterial mutagenesis and mouse skin carcinogenesis induced by 7, 12-dimethylbenz[a]anthracene.

Chung WY, Lee JM, Lee WY, et al.

Mutat Res. 2000 Dec 20; 472(1-2):139-45.

Porphyrins which are widespread in nature can interfere with the actions of certain carcinogens and mutagens, and have also been used clinically in photodynamic therapy (PDT) of tumors. Porphyrins such as chlorophyll, chlorophyllin (CHL) and hemin are known to inactivate various mutagens by forming complexes with them. Tetrakis(4-benzoic acid)porphyrin (TBAP) has been developed as a photosensitizer for PDT and its metal complex, MnTBAP has been shown to be efficacious in a variety of in vitro and in vivo oxidative stress models of human diseases. In the present study, we have found that TBAP and hemin exert concentration-related inhibition of his(+) reversion in Salmonella typhimurium TA100 induced by 7, 12-dimethylbenz[a]anthracene (DMBA), and significantly reduced both incidence and multiplicity of skin tumors when topically applied prior to treatment of 12-O-tetradecanoylphorbol-13-acetate in female ICR mice. Covalent DNA binding of DMBA in mouse skin was also significantly inhibited by topical application of TBAP or hemin as well as CHL. These results suggest the chemopreventive potential of compounds containing a porphyrin nucleus

Study of the forces of stabilizing complexes between chlorophylls and heterocyclic amine mutagens.

Dashwood R, Yamane S, Larsen R.

Environ Mol Mutagen. 1996; 27(3):211-8.

Chlorophyllin (CHL), a water-soluble derivative of chlorophyll, forms molecular complexes with heterocyclic amine mutagens in vitro. In a previous study [Dashwood and Guo (1993): *Environ Mol Mutagen*, 22:164-171], we observed an inverse correlation between the binding constants of several mutagen-CHL complexes and the antimutagenic potency of CHL in the Salmonella assay. The present investigation utilized molecular mechanics methods of energy minimization and spectrophotometric titration to examine structural features of chlorophylls, chlorins, and porphyrins that might be important for complex formation with heterocyclic amines. The exocyclic amine group of the mutagen aligned consistently with acid groups in CHL, suggesting that H-bond or electrostatic interactions facilitate complex formation. Replacement of the exocyclic amine with a nitro group abrogated this specific orientation and raised the minimized energies of the complexes. No relationship was found between complex strength and the specific positions of amine or methyl groups on the mutagen. However, the presence of methyl groups increased the minimized energies and lowered the binding constants of the complexes, perhaps due to partial disruption of pi-pi interaction by steric effects. All of the compounds examined, including chlorophyll a, required the presence of pi-pi interactions to form stable complexes with the heterocyclic amines. In general, the present results were in agreement with the inhibitory potency of each compound in the Salmonella assay, and they provide further support for the hypothesis that chlorophylls in the diet might act as interceptor molecules of food-borne carcinogens and mutagens

Chemopreventive properties of chlorophylls towards aflatoxin B1: a review of the antimutagenicity and anticarcinogenicity data in rainbow trout.

Dashwood R, Negishi T, Hayatsu H, et al.

Mutat Res. 1998 Mar 20; 399(2):245-53.

The anticarcinogenic activity of chlorophyllin (CHL), a water-soluble derivative of chlorophyll, was first reported in rainbow trout. This review describes certain experiments which set the stage for long-term tumor bioassays, in trout and other species, using CHL and various food-borne carcinogens. Initial work with trout and rat liver enzymes in the Salmonella assay showed that CHL

was a potent antimutagen towards heterocyclic amines, polycyclic aromatic hydrocarbons, aflatoxins and other classes of mutagen. Antimutagenic activity was further demonstrated using the corresponding direct-acting mutagens in the absence of an exogenous metabolizing system. Mutagen-inhibitor interaction (molecular complex formation) was identified in spectrophotometry studies, suggesting that CHL acts as an 'interceptor molecule'. In vivo, CHL reduced hepatic AFB1-DNA adducts and hepatocarcinogenesis when the inhibitor and carcinogen were co-administered in the diet. Finally, co-injection of inhibitor and AFB1 into trout embryos established that CHL was more effective than chlorophyll a in reducing AFB1-DNA adducts 2 weeks after injection, and liver tumors after 1 year

Identification and characterization of chlorin e(4) ethyl ester in sera of individuals participating in the chlorophyllin chemoprevention trial.

Egner PA, Stansbury KH, Snyder EP, et al.

Chem Res Toxicol. 2000 Sep; 13(9):900-6.

Chlorophyllin (CHL), a mixture of water soluble derivatives of chlorophyll, has been shown to be an effective inhibitor of aflatoxin B(1) (AFB(1)) carcinogenesis and AFB(1)-DNA adduct formation in rainbow trout and rats [Breinholt, V., Hendricks, J., Pereira, C., Arbogast, D., and Bailey, G. (1995) *Cancer Res.* 55, 57-62; Kensler, T. W., Groopman, J. D., and Roebuck, B. D. (1998) *Mutat. Res.* 402, 165-172]. The chemopreventive action of CHL has been previously attributed to molecular complexing. In 1997, a randomized, double-blind clinical trial of CHL was conducted in Qidong, Jiangsu Province, People's Republic of China. At the completion of the study, when serum samples were regrouped by subject identification number, it was noted that many of the participant samples were green in color. Using HPLC, ESI/MS, and MS/MS techniques, serum samples from individuals receiving CHL were found to contain previously unreported copper chlorin e(4) ethyl ester (CuCle(4) ethyl ester) as well as copper chlorin e(4) (CuCle(4)). Both chlorins originated in the study tablet, were absorbed into the bloodstream, and conferred a green color to the sera. This initial finding of in vivo absorption and bioavailability of two chlorin derivatives suggests that the mechanism of CHL chemoprevention may lie in the actions of these two components in vivo in addition to preventing carcinogen absorption from the gut

Chlorophyllin intervention reduces aflatoxin-DNA adducts in individuals at high risk for liver cancer.

Egner PA, Wang JB, Zhu YR, et al.

Proc Natl Acad Sci U S A. 2001 Dec 4; 98(25):14601-6.

Residents of Qidong, People's Republic of China, are at high risk for development of hepatocellular carcinoma, in part from consumption of foods contaminated with aflatoxins. Chlorophyllin, a mixture of semisynthetic, water-soluble derivatives of chlorophyll that is used as a food colorant and over-the-counter medicine, has been shown to be an effective inhibitor of aflatoxin hepatocarcinogenesis in animal models by blocking carcinogen bioavailability. In a randomized, double-blind, placebo-controlled chemoprevention trial, we tested whether chlorophyllin could alter the disposition of aflatoxin. One hundred and eighty healthy adults from Qidong were randomly assigned to ingest 100 mg of chlorophyllin or a placebo three times a day for 4 months. The primary endpoint was modulation of levels of aflatoxin-N(7)-guanine adducts in urine samples collected 3 months into the intervention measured by using sequential immunoaffinity chromatography and liquid chromatography-electrospray mass spectrometry. This aflatoxin-DNA adduct excretion product serves as a biomarker of the biologically effective dose of aflatoxin, and elevated levels are associated with increased risk of liver cancer. Adherence to the study protocol was outstanding, and no adverse events were reported. Aflatoxin-N(7)-guanine could be detected in 105 of 169 available samples. Chlorophyllin consumption at each meal led to an overall 55% reduction ($P = 0.036$) in median urinary levels of this aflatoxin biomarker compared with those taking placebo. Thus, prophylactic interventions with chlorophyllin or supplementation of diets with foods rich in chlorophylls may represent practical means to prevent the development of hepatocellular carcinoma or other environmentally induced cancers

Genetics of aging.

Finch CE, Tanzi RE.

Science. 1997 Oct 17; 278(5337):407-11.

The role of genetics in determining life-span is complex and paradoxical. Although the heritability of life-span is relatively minor, some genetic variants significantly modify senescence of mammals and invertebrates, with both positive and negative impacts on age-related disorders and life-spans. In certain examples, the gene variants alter metabolic pathways, which could thereby mediate interactions with nutritional and other environmental factors that influence life-span. Given the relatively minor effect and variable penetrance of genetic risk factors that appear to affect survival and health at advanced ages, life-style and other environmental influences may profoundly modify outcomes of aging

Cytochrome P-450 oxidations and the generation of biologically reactive intermediates.

Guengerich FP, Shimada T, Bondon A, et al.

Adv Exp Med Biol. 1991; 283:1-11.

Protection by chlorophyllin and indole-3-carbinol against 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP)-induced DNA adducts and colonic aberrant crypts in the F344 rat.

Guo D, Schut HA, Davis CD, et al.

Carcinogenesis. 1995 Dec; 16(12):2931-7.

The most abundant heterocyclic amine in fried ground beef, 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), induces colon carcinomas in the male F344 rat. The potential chemopreventive effects of two compounds, namely, the 'interceptor molecule' chlorophyllin (CHL) and a modulator of carcinogen activation, indole-3-carbinol (I3C), were examined in a PhIP colon carcinogenesis model. During weeks 3 and 4 of a 16-week study, F344 rats were given PhIP by oral gavage (50 mg/kg body weight, alternating days). Inhibitors were given either before and during PhIP exposure, after PhIP treatment, or continuously for 16 weeks. Treatment of rats with 0.1% CHL in the drinking water inhibited the formation of aberrant crypt foci (ACF) with $> \text{ or } = 4$ crypts/focus, from 1.4 \pm 0.9 in controls to 0.7 \pm 0.3 following post-initiation CHL treatment, and to 0.3 \pm 0.5 in rats given CHL continuously for 16 weeks (mean \pm SD; $P = 4$ crypts/focus). In a separate experiment, rats were given 0.1% CHL in the drinking water or 0.1% I3C in the diet for 4 weeks. At the end of week 3, animals received 50 mg PhIP/kg body weight by single oral gavage and PhIP-DNA adducts were quantified in the colon and several other tissues by ^{32}P -postlabeling analysis. In addition, the urine and feces were collected to study the effects of inhibitor treatment on PhIP metabolism and excretion. No significant protection against PhIP-DNA adduct formation was detected in the colon after CHL dosing, nor was a consistent pattern of CHL inhibition observed in several other tissues. In contrast, I3C shifted the time-course of adducts in all tissue; compared with controls, adducts were increased by I3C at 6 h but decreased at 24 h and 7 days following PhIP treatment. Analysis of urine metabolites revealed that I3C and CHL decreased the excretion of unmetabolized PhIP and 4'-hydroxy-PhIP but increased the phase II detoxification products PhIP-4'-O-glucuronide and PhIP-4'-sulfate. In the feces, the elimination of unmetabolized PhIP was increased from 54.5% in controls to approximately 67% in CHL-treated rats and decreased to 28% in rats given I3C ($P < 0.05$). These results support a protective role for CHL and I3C against PhIP-induced colon carcinogenesis through mechanisms which alter the uptake or metabolism of the carcinogen, and by suppression in the post-initiation phase.

Roads leading to breast cancer.

Haber D.

N Engl J Med. 2000 Nov 23; 343(21):1566-8.

Correlation between deoxyribonucleic acid excision-repair and life-span in a number of mammalian species.

Hart RW, Setlow RB.

Proc Natl Acad Sci U S A. 1974 Jun; 71(6):2169-73.

Effects of tea and chlorophyllin on the mutagenicity of N-hydroxy-IQ: studies of enzyme inhibition, molecular complex formation, and degradation/scavenging of the active metabolites.

Hernaiz J, Xu M, Dashwood R.

Environ Mol Mutagen. 1997; 30(4):468-74.

Green tea and black tea inhibit the formation of carcinogen-DNA adducts and colonic aberrant crypts in rats given 2-amino-3-methylimidazo[4,5-f]quinoline (IQ), a mutagen from cooked meat. The Salmonella mutagenicity assay was used in the present study to test individual constituents of tea as inhibitors of 2-hydroxyamino-3-methylimidazo[4,5-f]quinoline (N-hydroxy-IQ), a direct-acting metabolite of IQ. Testing of pure compounds at doses relevant to their levels in tea identified epigallocatechin (EGC) and epigallocatechin-3-gallate (EGCG) as the primary antimutagens. Studies of the inhibitory mechanisms established that the rate of degradation of N-hydroxy-IQ under aqueous conditions was not increased significantly in the presence of tea, in contrast to the results obtained with the complexing agent chlorophyllin (CHL), which rapidly degraded the mutagen. Interaction between N-hydroxy-IQ and several tea constituents was detected in spectrophotometric studies, but the binding constants were only on

the order of 1×10^3 M⁻¹, suggesting that mechanisms other than complex formation might prevail under the conditions of the Salmonella assay. Comparison of the results in two different strains of Salmonella typhimurium, TA98 and TA98/1,8-DNP6, indicated that the antimutagenic activity of EGCG was dependent, at least in part, on a functional O-acetyltransferase activity in the bacteria. These studies suggest that tea constituents inhibit the enzyme(s) which generate the aryl nitrenium ion and directly scavenge the reactive electrophile, whereas CHL complexes with heterocyclic amines and facilitates the degradation of active metabolites

The heritability of human longevity: a population-based study of 2872 Danish twin pairs born 1870-1900.

Herskind AM, McGue M, Holm NV, et al.

Hum Genet. 1996 Mar; 97(3):319-23.

The aim of this study was to explore, in a large and non-censored twin cohort, the nature (i.e., additive versus non-additive) and magnitude (i.e., heritability) of genetic influences on inter-individual differences in human longevity. The sample comprised all identified and traced non-emigrant like-sex twin pairs born in Denmark during the period 1870-1900 with a zygosity diagnosis and both members of the pairs surviving the age of 15 years. A total of 2872 pairs were included. Age at death was obtained from the Danish Central Person Register, the Danish Cause-of-Death Register and various other registers. The sample was almost non-censored on the date of the last follow-up (May 1, 1994), all but 0.6% had died, leaving a total of 2872 pairs for analysis. Proportions of variance attributable to genetic and environmental factors were assessed from variance-covariance matrices using the structural equation model approach. The most parsimonious explanation of the data was provided by a model that included genetic dominance (non-additive genetic effects caused by interaction within gene loci) and non-shared environmental factors (environmental factors that are individual-specific and not shared in a family). The heritability of longevity was estimated to be 0.26 for males and 0.23 for females. The small sex-difference was caused by a greater impact of non-shared environmental factors in the females. Heritability was found to be constant over the three 10-year birth cohorts included. Thus, longevity seems to be only moderately heritable. The nature of genetic influences on longevity is probably non-additive and environmental influences non-shared. There is no evidence for an impact of shared (family) environment

Effect of deodorants on halitosis.

Hideshi N.

Yakuzaigaku. 1996; 56(1):32-9.

Chlorophyllin as an effective antioxidant against membrane damage in vitro and ex vivo.

Kamat JP, Bloor KK, Devasagayam TP.

Biochim Biophys Acta. 2000 Sep 27; 1487(2-3):113-27.

Chlorophyllin (CHL), the sodium-copper salt and the water-soluble analogue of the ubiquitous green pigment chlorophyll, has been attributed to have several beneficial properties. Its antioxidant ability, however, has not been examined in detail. Using rat liver mitochondria as model system and various sources for the generation of reactive oxygen species (ROS) we have examined the membrane-protective properties of CHL both under in vitro and ex vivo conditions. Oxidative damage to proteins was assessed as inactivation of the enzymes, cytochrome c oxidase and succinic dehydrogenase besides formation of protein carbonyls. Damage to membrane lipids was measured by formation of lipid hydroperoxides and thiobarbituric acid reactive substances. The effect of this compound on the antioxidant defense system was studied by estimating the level of glutathione and superoxide dismutase. ROS were generated by gamma-radiation, photosensitization, ascorbate-Fe(2+), NADPH-ADP-Fe (3+) and the peroxy radical generating agent, azobis-amidopropane hydrochloride. Our results show that CHL is highly effective in protecting mitochondria, even at a low concentration of 10 microM. The antioxidant ability, at equimolar concentration, was more than that observed with ascorbic acid, glutathione, mannitol and tert-butanol. When CHL was fed to mice at a dose of 1% in drinking water, there was a significant reduction in the potential for oxidative damage in cell suspensions from liver, brain and testis. To examine the possible mechanisms responsible for the observed antioxidant ability we have studied the reaction of CHL with the potent ROS in the form of hydroxyl radical and singlet oxygen. The compound shows a fairly high rate constant with singlet oxygen, in the order of 1.3×10^8 M⁽⁻¹⁾ s⁽⁻¹⁾. In conclusion, our studies showed that CHL is a highly effective antioxidant, capable of protecting mitochondria against oxidative damage induced by various ROS

Use of aflatoxin adducts as intermediate endpoints to assess the efficacy of chemopreventive interventions in animals and man.

Kensler TW, Groopman JD, Roebuck BD.

Clinical cancer prevention studies that use disease as an endpoint are of necessity, large, lengthy, and extremely costly. Development of the field of cancer chemoprevention is being accelerated by the application of intermediate markers to preclinical and clinical studies. Sensitive and specific analytic methods have been developed for detecting and quantifying levels of covalent adducts of aflatoxins with cellular DNA and blood proteins at ambient levels of exposure. Such biomarkers can be applied to the preselection of exposed individuals for study cohorts, thereby reducing study size requirements. Levels of these aflatoxin-DNA and albumin adducts can be modulated by chemopreventive agents such as oltipraz and chlorophyllin in experimental models. Overall, a good concordance is seen between diminution of biomarkers and reductions in tumor incidence and/or multiplicity in these settings. Thus, these markers can also be used to rapidly assess the efficacy of preventive interventions. However, the successful application of these biomarkers to clinical prevention trials will be dependent upon prior determination of the associative or causal role of the marker to the carcinogenic process, establishment of the relationship between dose and response, and appreciation of the kinetics of adduct formation and removal. The general approach that has been utilized for the development, validation and application of aflatoxin-DNA and protein adduct biomarkers to cancer chemoprevention trials is summarized

Calories and cancer: can we starve our way to health?

Kuska B.

J Natl Cancer Inst. 2000 Sep 20; 92(18):1466-9.

Studies of Social, Biobehavioral, and Genetic Correlations.

Ljungquist S.

1995;(5)

Inhibitory effect of chlorophyllin on the frequency of sister chromatid exchanges produced by benzo[a]pyrene in vivo.

Madrigal-Bujaidar E, Velazquez-Guadarrama N, Diaz-Barriga S.

Mutat Res. 1997 Jan 15; 388(1):79-83.

The study was designed to determine the antigenotoxic potential of chlorophyllin (Chl), against the frequency of sister-chromatid exchanges (SCE) produced by benzo[a]pyrene (B[a]P) in vivo. We used the mouse bone marrow test system to measure the effect of a single injection of the compounds: 40 mg/kg of B[a]P, and 1 h later, 1.0, 2.0, 4.0 and 8.0 mg/kg of Chl. As controls we included both chemicals using the dosages mentioned above as well as mineral oil (0.25 mg/kg). The results indicated the following: (1) Chl per se was not genotoxic, showing SCE values in the range of the control level; (2) B[a]P increased the rate of SCEs three times in relation to the basal level; (3) the SCE level produced with B[a]P was diminished by all 4 doses of Chl, but better results were obtained with 2-4 mg/kg, a range which induced Inhibition Indices of 80.9% and 77.5% respectively; (4) the Average Generation Time Index was not modified by the compounds used in the experiment; and (5) the Mitotic Index also showed no significant modification induced by the chemicals, with respect to the control value

Nutrition interventions in aging and age-associated disease.

Meydani M.

Ann N Y Acad Sci. 2001 Apr; 928:226-35.

The nutritional status and needs of elderly people are associated with age-related biological and often socioeconomic changes. Decreased food intake, a sedentary lifestyle, and reduced energy expenditure in older adults altogether become critical risk factors for malnutrition, especially protein and micronutrients. Surveys indicate that the elderly are particularly at risk for marginal deficiency of vitamins and trace elements. Changes in bodily functions, together with the malnutrition associated with advancing age, increase the risk of developing a number of age-related diseases. Chronic conditions pose difficulties for the elderly in carrying out the activities of daily living and may increase the requirements for certain nutrients due to changes in absorptive and metabolic capacity. Free radicals and oxidative stress have been recognized as important factors in the biology of aging and of many age-associated degenerative diseases. In this regard, modulation of oxidative stress by calorie restriction, as demonstrated in animal models, is suggested as one mechanism to slow the aging process and the decline of body functions. Therefore, dietary components with antioxidant activity have received particular attention because of their potential role in modulating oxidative stress associated with aging and chronic conditions. Several studies have indicated potential roles for

dietary antioxidants in the reduction of degenerative disease such as vascular dementia, cardiovascular disease, and cancer. In support of epidemiological studies, our recent studies indicate that the antioxidant properties of vitamin E and polyphenols present in green tea may contribute to reducing the risk of cardiovascular disease, in part by reducing the susceptibility of low density lipoproteins to oxidation, decreasing the vascular endothelial cell expression of pro-inflammatory cytokines, and decreasing the expression of adhesion molecules and monocyte adhesion. Recently, we also demonstrated that these dietary antioxidants may have a preventive role in cancer, potentially through the suppression of angiogenesis by inhibiting interleukin-8 production and the cell junction molecule VE-cadherin. These findings concur with epidemiologic, clinical, and animal studies suggesting that the consumption of green tea and vitamin E is associated with a reduced risk of cardiovascular disease and cancer, the leading causes of morbidity and mortality among the elderly

Antigenotoxic activity of natural chlorophylls.

Negishi T, Rai H, Hayatsu H.

Mutat Res. 1997 May 12; 376(1-2):97-100.

Chlorophyllin, a man-made water-soluble form of chlorophyll, is a focus of intensive studies from many laboratories for its antimutagenic and anticarcinogenic properties. Natural chlorophylls, in contrast, have been little studied in this regard. Since yellow-green vegetables are implicated to be protective against human cancers by epidemiological studies, it is important to explore the antigenotoxic properties of natural chlorophylls. Previously, we reported that a chlorophyll sample prepared from *Chlorella vulgaris* inhibited the mutagenicity of 3-hydroxyamino-1-methyl-5H-pyrido[4,3-b]indole, a direct-acting mutagen, in *Salmonella*, and that the chlorophyll also showed inhibition of wing spot formation in *Drosophila* induced by 3-amino-1-methyl-5H-pyrido[4,3-b]indole (Trp-P-2). We have now prepared several samples of chlorophyll from spinach and chlorella, and studied their effect on the genotoxicity of 4-nitroquinoline 1-oxide (4NQO) in *Drosophila*. The results showed that the genotoxicity of orally given 4NQO was suppressed by simultaneous administration of the chlorophylls. The mechanisms of this inhibition are discussed

Comparative antimutagenicity of 5 compounds against 5 mutagenic complex mixtures in *Salmonella typhimurium* strain TA98.

Ong T, Whong WZ, Stewart JD, et al.

Mutat Res. 1989 Jan; 222(1):19-25.

Using the Ames *Salmonella*/microsome assay, we compared the antimutagenic activities of chlorophyllin, retinol, beta-carotene, vitamin C, and vitamin E against solvent extracts of coal dust, diesel emission particles, airborne particles, fried beef, and tobacco snuff. The results show that chlorophyllin inhibited 69% of the mutagenic activity of tobacco snuff and over 90% of that of the other 4 complex mixtures. Retinol inhibited 29-48% of the mutagenic activity of all 5 complex mixtures. beta-Carotene, vitamin C, and vitamin E inhibited, if any, less than 39% of the activity of the complex mixtures studied. Vitamin C enhanced the mutagenicity of airborne particles. These results indicate that for these dietary and environmental complex mixtures chlorophyllin is a more effective antimutagen than retinol, beta-carotene, vitamin C, and vitamin E

Chlorophyllin: a potent antimutagen against environmental and dietary complex mixtures.

Ong TM, Whong WZ, Stewart J, et al.

Mutat Res. 1986 Feb; 173(2):111-5.

Chlorophyllin, the sodium and copper salt of chlorophyll, was tested for its ability to inhibit the mutagenic activity of a variety of complex mixtures--extracts of fried beef, fried shredded pork, red grape juice, red wine, cigarette smoke, tobacco snuff, chewing tobacco, airborne particles, coal dust and diesel emission particles--in strain TA98 of *Salmonella typhimurium*. Chlorophyllin was highly effective against the mutagenicity (90-100% inhibition) of 8 of these 10 mixtures. The mutagenicity of the other 2 mixtures was inhibited 75-80% at the highest concentration of chlorophyllin studied. Control and reconstruction experiments showed that chlorophyllin was not toxic to *Salmonella* at the concentrations used. The antimutagenic activity of chlorophyllin was heat-stable. The mechanism of the antimutagenicity of chlorophyllin in these experiments is not known; however, chlorophyllin is an antioxidant. Scavenging of radicals and/or interaction with the active group of mutagenic compounds may be responsible for its antimutagenic activity. The data reported here indicate that chlorophyllin is potentially useful as an antimutagenic agent

Selenomethionine induction of DNA repair response in human fibroblasts.

Seo YR, Sweeney C, Smith ML.

Selenium compounds have a long history in chemoprevention of mammary and colon cancers in rodent models. Selenium compounds are in current clinical trials, having shown promise in prevention of prostate and other human cancers. In human tissues, it has been estimated that each cell sustains approximately 10 000 potentially mutagenic (if not repaired) lesions per day due to endogenous DNA damage. Almost no studies have addressed the potential for selenium compounds to induce DNA repair, a potential mechanism for their cancer-preventive actions. We show that selenium in the form of selenomethionine induces a DNA repair response in normal human fibroblasts in vitro, and protects cells from DNA damage. We show a possible mechanism for the inducible DNA repair response, in which enhanced repair complex formation was observed in selenomethionine-treated cells

Effect of chemopreventive agents on DNA adduction induced by the potent mammary carcinogen dibenzo[a,l]pyrene in the human breast cells MCF-7.

Smith WA, Freeman JW, Gupta RC.

Mutat Res. 2001 Sep 1; 480-481:97-108.

Over 1500 structurally diverse chemicals have been identified which have potential cancer chemopreventive properties. The efficacy and mechanisms of this growing list of chemoprotective agents may be studied using short-term bioassays that employ relevant end-points of the carcinogenic process. In this study, we have examined the effects of eight potential chemopreventive agents, N-acetylcysteine (NAC), benzylicyanate (BIC), chlorophyllin, curcumin, 1,2-dithiole-3-thione (D3T), ellagic acid, genistein, and oltipraz, on DNA adduction of the potent mammary carcinogen dibenzo[a,l]pyrene (DBP) using the human breast cell line MCF-7. Bioactivation of DBP by MCF-7 cells resulted in the formation of one predominant (55%) dA-derived and several other dA- or dG-derived DNA adducts. Three test agents, oltipraz, D3T, and chlorophyllin substantially (>65%) inhibited DBP-DNA adduction at the highest dose tested (30 microM). These agents also significantly inhibited DBP adduct levels at a lower dose of 15 microM, while oltipraz was effective even at the lowest dose of 5 microM. Two other agents, genistein and ellagic acid were moderate (45%) DBP-DNA adduct inhibitors at the highest dose tested, while NAC, curcumin, and BIC were ineffective. These studies indicate that the MCF-7 cell line is an applicable model to study the efficacy of cancer chemopreventive agents in a human setting. Moreover, this model may also provide information regarding the effect of the test agents on carcinogen bioactivation and detoxification enzymes

Mutagenic consequences of the alteration of DNA by chemicals and radiation.

Strauss B, Turkington E, Wang J, et al.

Adv Exp Med Biol. 1991; 283:211-23.

Inhibitory effect of chlorophyllin on diethylnitrosamine and phenobarbital-induced hepatocarcinogenesis in male F344 rats.

Sugie S, Okamoto K, Makita H, et al.

Jpn J Cancer Res. 1996 Oct; 87(10):1045-51.

Modifying effects of chlorophyllin (CHL) on the diethylnitrosamine (DEN)-phenobarbital (PB) hepatocarcinogenesis model were examined in rats. Five-week-old male F344 rats were divided into 8 groups. Groups 1 through 5 were given i.p. injections of DEN (100 mg/kg body weight) once a week for 3 weeks beginning one week after the start of the experiment, while groups 6 through 8 received vehicle treatment. Groups 1, 2, 3 and 7 received drinking water with 500 ppm PB from one week after the end of carcinogen or vehicle treatment. CHL-containing diet (2000 ppm) was given to group 2 during the initiation phase and to groups 3 and 5 during the promotion and the post-initiation phase, respectively. Group 6 was given the experimental diet alone throughout the experiment (24 weeks). Liver neoplasms were present in DEN-treated groups and PB treatment promoted liver tumorigenesis. The incidences of adenoma in groups 2 and 3 were significantly smaller than in group 1 ($P<0.05$ and $P<0.02$), although the reductions in the incidences of liver cell cancer were not significant. The average numbers of liver neoplasms/rat in group 2 were significantly smaller than in group 1 ($P<0.05$ - $P<0.005$). Glutathione S-transferase placental form-positive foci were also significantly decreased by CHL treatment ($P<0.05$ and $P<0.001$). DEN and PB exposure increased liver ornithine decarboxylase activity and this increase was significantly inhibited by feeding of CHL during the initiation phase ($P<0.001$). These results suggest that CHL is a chemopreventive agent for liver neoplasia

Mechanisms of the in vitro antimutagenic action of chlorophyllin against benzo[a]pyrene: studies of enzyme inhibition, molecular complex formation and degradation of the ultimate carcinogen.

Mutat Res. 1994 Jul 16; 308(2):191-203.

Mechanisms of the antimutagenic action of chlorophyllin (CHL) towards benzo[a]pyrene (BP) were studied in vitro. In the Salmonella assay, CHL inhibited the mutagenic activity of BP in the presence of an S9 activation system and was particularly effective against the direct-acting ultimate carcinogen, benzo[a]pyrene-7,8-dihydrodiol-9,10-epoxide (BPDE). Spectral studies indicated that the time-dependent hydrolysis of BPDE to tetrols was augmented in the presence of CHL concentrations on the order of 5 microM. Dose-related inhibition of several cytochrome P450-dependent enzyme activities was observed upon addition of CHL to in vitro incubations. Spectral changes for the interaction between CHL and cytochrome P450 indicated that CHL does not bind to the active site of the enzyme, but exerts its inhibitory effect indirectly. This was achieved by inhibiting NADPH-cytochrome P450 reductase (K_i approximately 120 microM with cytochrome c as substrate), and did not involve lowering of the effective substrate concentration by complex formation with the procarcinogen. It is concluded that the in vitro antimutagenic activity of CHL towards BP involves accelerated degradation of the ultimate carcinogen, with inhibition of carcinogen activation occurring only at high CHL concentrations. The latter mechanism is unlikely to occur in vivo following p.o. administration due to the limited uptake of CHL from the gut, but tissue concentrations may be sufficiently high to cause degradation of BPDE

Inhibition of the mutagenicity of 2-nitrofluorene, 3-nitrofluoranthene and 1-nitropyrene by vitamins, porphyrins and related compounds, and vegetable and fruit juices and solvent extracts.

Tang X, Edenharder R.

Food Chem Toxicol. 1997 Mar; 35(3-4):373-8.

When 21 vitamins including related compounds haemin, chlorophyllin, chlorophyll, biliverdin and bilirubin, as well as juices from five fruits and 25 vegetables and solvent extracts from the residues of fruits and vegetables were tested for their antimutagenic potencies with respect to mutagenicity induced by 2-nitrofluorene (2-NF), 3-nitrofluoranthene (3-NFA) and 1-nitropyrene(1-NP) in Salmonella typhimurium TA98 the following results were obtained. The tetracyclic nitroarenes 3-NFA and 1-NP were in general more effectively antagonized by potent antimutagenic compounds than the tricyclic 2-NF. beta-Carotene, retinol, retinal, retinoic acid, retinol palmitate, riboflavin 5'-phosphate, alpha-tocopherol, vitamins B12, C, K1 and K3 as well as biliverdin, bilirubin, chlorophyll, chlorophyllin and haemin exerted antimutagenicity against the nitroarenes cited previously. All other vitamins were inactive. While part of the juices were inactive, juices from cauliflower, carrots, chives, radishes and spinach exerted weak antimutagenic activities. However, weak to moderate co-mutagenic effects were seen with grapes, kiwi, pineapple, eggplant, celeriac, chicory greens, fennel leaves and radishes and strong effects with peppers which were not caused by the presence of growth-promoting factors. Most solvent fractions were inactive but fractions containing chlorophyll exerted antimutagenicity

Dietary intake of heterocyclic amines and cancers of the esophagus and gastric cardia.

Terry PD, Lagergren J, Wolk A, et al.

Cancer Epidemiol Biomarkers Prev. 2003 Sep; 12(9):940-4.

The results of two epidemiological studies suggest that high intake of heterocyclic amines, which are formed on the surface of meats cooked at high temperatures, might be associated with increased risk of esophageal or cardia cancers. Our aim was to further investigate heterocyclic amine intake and risk of these cancers. We examined data from a nationwide, population-based, case-control study of risk factors for adenocarcinoma of the esophagus and gastric cardia and squamous cell carcinoma of the esophagus in Sweden, with 185, 258, and 165 cases, respectively, and 815 controls. Heterocyclic amine intake was estimated based on the frequency of consumption and degree of surface browning of commonly fried meats, and the consumption of pan juices. Statistically nonsignificant 50-70% higher risks of esophageal squamous cell carcinoma were observed among individuals in the highest quartile levels of 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline, 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline, and 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine relative to those in the lowest. Dose-risk trends were evident. Subjects reporting high intake of all three heterocyclic amines had an odds ratio of 2.4 (95% confidence interval, 1.2-4.8) relative to those with low intake of all three substances. In contrast, no association was found with risk of adenocarcinoma of the esophagus or gastric cardia. Heterocyclic amine intake might be associated with an increase in risk of squamous cell carcinoma of the esophagus. Given the dearth of epidemiological data regarding these cancers and the lack of established biological mechanisms, confirmatory data are needed

Effects of Sasa Health, extract of bamboo grass leaves, on spontaneous mammary tumourigenesis in SHN mice.

Tsunoda S, Yamamoto K, Sakamoto S, et al.

Chronic treatment with Sasa Health, extract of bamboo grass leaves obtained by alkaline hydrolysis, in drinking water at the concentration of 0.044%-0.088% Fe-Chlorophyllin Na resulted in the significant inhibition of both development and growth of spontaneous mammary tumours in a high mammary tumour strain of SHN virgin mice. Limited treatment for 12 days in mice with palpable sizes of mammary tumours also markedly retarded the growth of the tumours. The end-bud formation and thymidylate synthetase activity of normal mammary glands were stimulated, but the formation of preneoplastic mammary hyperplastic alveolar nodules was inhibited by the treatment. Chronic ingestion of Sasa Health stimulated the excretion of urine components and decreased and increased the prolactin level and superoxide dismutase activity in serum, respectively. It showed no deleterious effects on food and water intake, body growth and any external appearance and all findings indicate that Sasa Health could be a promising agent for the protection and therapy of breast and other types of tumours

Heterocyclic aromatic amine metabolism, DNA adduct formation, mutagenesis, and carcinogenesis.

Turesky RJ.

Drug Metab Rev. 2002 Aug; 34(3):625-50.

Heterocyclic aromatic amines (HAAs) are carcinogenic compounds formed in meats, fish, and poultry prepared under common household cooking practices. Some HAAs are also formed in tobacco smoke condensate. Because of the widespread occurrence of HAAs in these daily staples, health concerns have been raised regarding the potential role of HAAs in the etiology of some human cancers associated with frequent consumption of these products. In this review, the metabolism of HAAs to biologically active metabolites that bind to DNA and provoke mutations and cancer in various biological systems is discussed. Some of the current analytical and molecular methods that are used to measure biomarkers of HAA exposure and genetic damage in experimental animal models and humans are also presented. These biochemical data combined may help to better assess the role that HAAs may have in the development of some common forms of human cancers

Effect of tea catechins for halitosis and their application to chewing gum.

Ui M.

J Jpn Soc Food Sci Technol. 1991; 38(12):1098-102.

Mitochondrial theory of aging matures--roles of mtDNA mutation and oxidative stress in human aging.

Wei YH, Ma YS, Lee HC, et al.

Zhonghua Yi Xue Za Zhi (Taipei). 2001 May; 64(5):259-70.

Mitochondrial theory of aging, a variant of free radical theory of aging, proposes that accumulation of damage to mitochondria and mitochondrial DNA (mtDNA) leads to aging of humans and animals. It has been supported by the observation that mitochondrial function declines and mtDNA mutation increases in tissue cells in an age-dependent manner. Age-related impairment in the respiratory enzymes not only decreases ATP synthesis but also enhances production of reactive oxygen species (ROS) through increased electron leakage in the respiratory chain. Human mtDNA, which is not protected by histones and yet is exposed to high levels of ROS and free radicals in the matrix of mitochondria, is susceptible to oxidative damage and mutation in tissue cells. In the past decade, more than one hundred mtDNA mutations have been found in patients with mitochondrial disease, and some of them also occur in aging human tissues. The incidence and abundance of these mutant mtDNAs are increased with age, particularly in tissues with great demand for energy. On the other hand, recent studies have revealed that the ability of the human cell to cope with oxidative stress is compromised in aging. Comparative analysis of gene expression by microarray technology has shown that a number of genes related to oxidative stress response are altered in aging animals. We discovered that the transcripts of early growth response protein-1, growth arrest and DNA damage-inducible proteins and glutathione S-transferase genes are increased in response to oxidative stress in human skin fibroblasts. Moreover, the activities of Cu,Zn-SOD, catalase and glutathione peroxidase decrease with age, whereas Mn-SOD activity increases with age up to 65 years and slightly declines thereafter in skin fibroblasts. Such an imbalance in the function of antioxidant enzymes may result in excess production of damaging ROS in the cell. This notion is supported by the observation that intracellular levels of H₂O₂ and oxidative damage to DNA and lipids are significantly increased with age of the fibroblast donor. Furthermore, the mitochondrial pool of reduced glutathione declines and DNA damage is enhanced in aging tissues. Taken together, these observations and our previous findings that mtDNA mutations and oxidative damage are increased in aging human tissues suggest that mitochondrial theory of aging is mature

Calories and cancer.

Winick M.

Hematol Oncol Clin North Am. 1991 Feb; 5(1):1-6.

The author presents the hypothesis that no single nutrient or class of food by itself significantly affects risk for most cancers. Rather, it is the dietary pattern or the mix of nutrients and foods that affects cancer risk. And the overall caloric intake or perhaps the caloric balance is central to whether a particular dietary pattern will affect cancer risk. Supporting evidence for this hypothesis, as well as implications if correct, is also presented

Well-done meat intake and the risk of breast cancer.

Zheng W, Gustafson DR, Sinha R, et al.

J Natl Cancer Inst. 1998 Nov 18; 90(22):1724-9.

BACKGROUND: Heterocyclic amines, mutagens formed in meats cooked at high temperatures, have been demonstrated as mammary carcinogens in animals. We conducted a nested, case-control study among 41836 cohort members of the Iowa Women's Health Study to evaluate the potential role of heterocyclic amines and intake of well-done meat in the risk for human breast cancer. **METHODS:** A questionnaire was mailed to individuals in the cohort who had breast cancer diagnosed during the period from 1992 through 1994 and a random sample of cancer-free cohort members to obtain information on usual intake of meats and on meat preparation practices. Color photographs showing various doneness levels of hamburger, beefsteak, and bacon were included. Multivariate analysis was performed on data from 273 case subjects and 657 control subjects who completed the survey. **RESULTS:** A dose-response relationship was found between doneness levels of meat consumed and breast cancer risk. The adjusted odds ratios (ORs) for very well-done meat versus rare or medium-done meat were 1.54 (95% confidence interval [CI]=0.96-2.47) for hamburger, 2.21 (95% CI=1.30-3.77) for beef steak, and 1.64 (95% CI=0.92-2.93) for bacon. Women who consumed these three meats consistently very well done had a 4.62 times higher risk (95% CI=1.36-15.70) than that of women who consumed the meats rare or medium done. Risk of breast cancer was also elevated with increasing intake of well-done to very well-done meat. **CONCLUSIONS:** Consumption of well-done meats and, thus, exposures to heterocyclic amines (or other compounds) formed during high-temperature cooking may play an important role in the risk of breast cancer

All Contents Copyright © 1995-2009 Life Extension Foundation All rights reserved.

LifeExtension®

These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease. The information provided on this site is for informational purposes only and is not intended as a substitute for advice from your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.