

## JOURNAL ABSTRACTS

### CoQ10 and Cancer

#### **COENZYME Q10: ITS BIOSYNTHESIS AND BIOLOGICAL SIGNIFICANCE IN ANIMAL ORGANISMS AND IN HUMANS.**

Coenzyme Q10 (ubiquinone) is a naturally occurring compound widely distributed in animal organisms and in humans. The primary compounds involved in the biosynthesis of ubiquinone are 4-hydroxybenzoate and the polyprenyl chain. An essential role of coenzyme Q10 is as an electron carrier in the mitochondrial respiratory chain. Moreover, coenzyme Q10 is one of the most important lipophilic antioxidants, preventing the generation of free radicals as well as oxidative modifications of proteins, lipids, and DNA, it and can also regenerate the other powerful lipophilic antioxidant, alpha-tocopherol. Antioxidant action is a property of the reduced form of coenzyme Q10, ubiquinol (CoQ10H<sub>2</sub>), and the ubisemiquinone radical (CoQ10H<sup>\*</sup>). Paradoxically, independently of the known antioxidant properties of coenzyme Q10, the ubisemiquinone radical anion (CoQ10<sup>-</sup>) possesses prooxidative properties. Decreased levels of coenzyme Q10 in humans are observed in many pathologies (e.g. cardiac disorders, neurodegenerative diseases, AIDS, cancer) associated with intensive generation of free radicals and their action on cells and tissues. In these cases, treatment involves pharmaceutical supplementation or increased consumption of coenzyme Q10 with meals as well as treatment with suitable chemical compounds (i.e. folic acid or B-group vitamins) which significantly increase ubiquinone biosynthesis in the organism. Estimation of coenzyme Q10 deficiency and efficiency of its supplementation requires a determination of ubiquinone levels in the organism. Therefore, highly selective and sensitive methods must be applied, such as HPLC with UV or coulometric detection.

Postepy Hig Med Dosw. 2005;59:150-9

#### **ROLE OF ANTIOXIDANTS IN PROPHYLAXIS AND THERAPY: A PHARMACEUTICAL PERSPECTIVE.**

Antioxidants are emerging as prophylactic and therapeutic agents. These are the agents, which scavenge free radicals otherwise reactive oxygen species and prevent the damage caused by them. Free radicals have been associated with pathogenesis of various disorders like cancer, diabetes, cardiovascular diseases, autoimmune diseases, neurodegenerative disorders and are implicated in aging. Several antioxidants like SOD, CAT, epigallocatechin-3-O-gallate, lycopene, ellagic acid, coenzyme Q10, indole-3-carbinol, genistein, quercetin, vitamin C and vitamin E have been found to be pharmacologically active as prophylactic and therapeutic agents for above mentioned diseases. Antioxidants are part of diet but their bioavailability through dietary supplementation depends on several factors. This major drawback of dietary agents may be due to one or many of the several factors like poor solubility, inefficient permeability, instability due to storage of food, first pass effect and GI degradation. Conventional dosage forms may not result in efficient formulation owing to their poor biopharmaceutical properties. Principles of novel drug delivery systems need to be applied to significantly improve the performance of antioxidants. Novel drug delivery systems (NDDS) would also help in delivery of these antioxidants by oral route, as this route is of prime importance when antioxidants are intended for prophylactic purpose. Implication of NDDS for the delivery of antioxidants is largely governed by physicochemical characteristics, biopharmaceutical properties and pharmacokinetic parameters of the antioxidant to be formulated. Recently, chemical modifications, coupling agents, liposomes, microparticles, nanoparticles and gel-based systems have been explored for the delivery of these difficult to deliver molecules. Results from several studies conducted across the globe are positive and provided us with new anticipation for the improvement of human healthcare.

J Control Release. 2006 Jul 20;113(3):189-207

#### **ADRIAMYCIN-INDUCED INTERFERENCE WITH CARDIAC MITOCHONDRIAL CALCIUM HOMEOSTASIS.**

Adriamycin (doxorubicin) is a potent and broad-spectrum antineoplastic agent, the clinical utility of which is limited by the development of a cumulative and irreversible cardiomyopathy. Although the drug affects numerous structures in different cell types, the mitochondrion appears to a principal subcellular target for the development of cardiomyopathy. This review describes evidence demonstrating that adriamycin redox cycles on complex I of the mitochondrial electron transport chain to liberate highly reactive free radical species of molecular oxygen. The primary effect of adriamycin on mitochondrial performance is the interference with oxidative phosphorylation and inhibition of ATP synthesis. Free radicals liberated from adriamycin redox cycling

are thought to be responsible for many of adriamycin, including lipid peroxidation, the oxidation of both proteins and DNA, and the depletion of glutathione and pyridine nucleotide reducing equivalents in the cell. It is this altered redox status that is believed to cause assorted changes in intracellular regulation, including the induction of the mitochondrial permeability transition and complete loss of mitochondrial integrity and function. Associated with this is the interference with mitochondrial-mediated cell calcium signaling, which is implicated as essential to the capacity of mitochondria to participate in bioenergetic regulation in response to external signals reflecting changes in metabolic demand. If taken to an extreme, this loss of mitochondrial plasticity may manifest in the liberation of signals mediating either oncotic or necrotic cell death, further perpetuating the cardiac failure associated with adriamycin-induced mitochondrial cardiomyopathy.

Cardiovasc Toxicol. 2007;7(2):101-7

### **COMBINED EFFICACY OF TAMOXIFEN AND COENZYME Q10 ON THE STATUS OF LIPID PEROXIDATION AND ANTIOXIDANTS IN DMBA INDUCED BREAST CANCER.**

An increasing amount of experimental and epidemiological evidence implicates the involvement of oxygen derived radicals in the pathogenesis of cancer development. It is well known that chemical carcinogenesis is multistage process. Free radicals are found to be involved in both initiation and promotion of multistage carcinogenesis. Tamoxifen (TAM) is a potent antioxidant and a non-steroidal antiestrogen drug most used in the chemotherapy and chemoprevention of breast cancer. Besides its anticarcinogenic potential, it also produces some adverse toxic side effects, while taken for a long time. In order to minimise the side effects and to improve the antioxidant efficacy of tamoxifen, coenzyme Q10 (CoQ10) was added. Hence the present study was designed to investigate the combined efficacy of TAM along with CoQ10 in 7, 12 dimethyl benz(a)anthracene (DMBA) induced peroxidative damage in rat mammary carcinoma. The experimental setup comprised of one control and five experimental groups and it was carried out in adult female Sprague-Dawley rats. Mammary carcinoma was induced by oral administration of DMBA (25 mg kg<sup>-1</sup> body wt) and the treatment was started by the oral administration of TAM (10 mg kg<sup>-1</sup> body wt day<sup>-1</sup>) and CoQ10 (40 mg kg<sup>-1</sup> body wt day<sup>-1</sup>) dissolved in olive oil and continued for 28 days. Rats induced with DMBA showed a decline in the thiol capacity of the cell accompanied by high malondialdehyde content levels along with lowered activities of antioxidant status (superoxide dismutase,

catalase, glutathione peroxidase and reduced glutathione). In contrast, glutathione metabolising enzymes (glutathione reductase, glucose-6-phosphate dehydrogenase and glutathione-S-transferase) were increased significantly in chemically induced carcinoma bearing rats. Administration of TAM along with CoQ10 restored the activities to a significant level thereby preventing cancer cell proliferation. This study highlights the increased antioxidant enzyme activities in relation to the susceptibility of cells to carcinogenic agents and the response of tumour cells to the chemotherapeutic agents.

Mol Cell Biochem. 2005 May;273(1-2):151-60

### **MUTUAL CROSS-TALK BETWEEN REACTIVE OXYGEN SPECIES AND NUCLEAR FACTOR-KAPPA B: MOLECULAR BASIS AND BIOLOGICAL SIGNIFICANCE.**

Reactive oxygen species (ROS) are emerging as key effectors in signal transduction. This role of ROS is especially evident in the pathways leading to programmed cell death (PCD) elicited in response to certain stress stimuli and cytokines. In these pathways, cytotoxic ROS signaling appears to be mediated in part by activation of the c-Jun-N-terminal kinase (JNK) mitogen-activated protein kinase (MAPK) cascade. Another pathway that is under ROS-mediated control in some systems is that leading to activation of transcription factor nuclear factor-kappa B (NF-kappaB), which is a central regulator of immunity, inflammation and cell survival. Remarkably, new evidence has unveiled the existence of a reciprocal, negative control that NF-kappaB exerts on ROS and JNK activities. This NF-kappaB-imposed restraint on ROS and JNK signaling is crucial for antagonism of PCD elicited by the proinflammatory cytokine tumor necrosis factor (TNF)alpha and likely other triggers. Effectors of this antagonistic cross-talk between NF-kappaB and ROS/JNK pathways have recently been identified. Because of the key roles that the prosurvival function of NF-kappaB plays in organismal physiology and disease, gaining a further mechanistic understanding of this cross-talk and NF-kappaB-dependent survival may be key to developing new therapies for the treatment of widespread human illnesses, such as cancer and chronic inflammatory conditions.

Oncogene. 2006 Oct 30;25(51):6731-48

### **THE NF-KAPPAB-MEDIATED CONTROL OF THE JNK CASCADE IN THE ANTAGONISM OF PROGRAMMED CELL DEATH IN HEALTH AND DISEASE.**

NF-kappaB/Rel transcription factors have recently emerged as crucial regulators of cell survival. Activation of NF-kappaB antagonizes programmed cell death (PCD) induced by tumor necrosis factor-receptors (TNF-Rs) and several other triggers. This prosurvival activity of NF-kappaB participates in a wide range of biological processes, including immunity, lymphopoiesis and development. It is also crucial for pathogenesis of various cancers, chronic inflammation and certain hereditary disorders. This participation of NF-kappaB in survival signaling often involves an antagonism of PCD triggered by TNF-R-family receptors, and is

mediated through a suppression of the formation of reactive oxygen species (ROS) and a control of sustained activation of the Jun-N-terminal kinase (JNK) cascade. Effectors of this antagonistic activity of NF-kappaB on this ROS/JNK pathway have been recently identified. Indeed, further delineating the mechanisms by which NF-kappaB promotes cell survival might hold the key to developing new highly effective therapies for treatment of widespread human diseases.

Cell Death Differ. 2006 May;13(5):712-29

### **ENERGY-MODULATING VITAMINS—A NEW COMBINATORIAL THERAPY PREVENTS CANCER CACHEXIA IN RAT MAMMARY CARCINOMA.**

Mitochondria are the major intracellular organelles producing ATP molecules via the electron transport chain. Cancer cells have a deviant energy metabolism, and a high rate of glycolysis is related to a high degree of dedifferentiation and proliferation. The overall net ATP production is diminished with cancer, which ultimately leads to cancer cachexia. The present study was designed to investigate the altered energy metabolism in cancer cells and to enhance ATP production in the normal host cell metabolism by enhancing the activities of mitochondrial enzymes, using energy-modulating vitamins, and thus prevent cancer cachexia. Female Sprague-Dawley rats were selected for the experimental study. Mammary carcinoma was induced by the oral administration of 7,12-dimethylbenz[a]anthracene (25 mg/kg body weight), and treatment was started by the oral administration of the energy-modulating vitamins riboflavin (45 mg/kg body weight per d), niacin (100 mg/kg body weight per d) and coenzyme Q10 (40 mg/kg body weight per d) for 28 d. Mitochondria were isolated from the mammary gland and liver of all four groups, and the Krebs cycle and oxidative phosphorylation enzymes were assayed. In mammary carcinoma-bearing animals, the activities of the Krebs cycle and oxidative phosphorylation enzymes were significantly decreased. These activities were restored to a greater extent in animals treated with energy-modulating vitamins. From these experimental results, one may hypothesize that the combination therapy of energy-modulating vitamins could be of major therapeutic value in breast cancer.

Br J Nutr. 2005 Jun;93(6):901-9

### **SUPPRESSION OF AZOXYMETHANE-INDUCED COLONIC PREMALIGNANT LESION FORMATION BY COENZYME Q10 IN RATS.**

Reactive oxygen species cause damage to proteins, lipids and DNA. Coenzyme Q10 (CoQ10) is a compound with mitochondrial bioenergetic functions. The reduced form of CoQ10 shows antioxidant activity. In the present study, effects of CoQ10 on development of azoxymethane (AOM)-induced aberrant crypt foci (ACF) and mucin-depleted foci (MDF) in F344 male rats were investigated. To induce ACF and MDF, 6-week old rats were given two weekly subcutaneous injections of AOM (15 mg/kg body weight) and also received a control diet or experimental diets containing CoQ10 (200 or 500 ppm) for 4 weeks, starting one day before the first dose of AOM. At 10 weeks of age, all animals were sacrificed and their colons were evaluated for numbers and sizes of ACF and MDF. Administration of 200 and 500 ppm CoQ10 resulted in reduction of ACF numbers, to 77% and 68% of the carcinogen control value, respectively. The percentages of ACF consisting of more than 4 crypts in these groups were also significantly lower than in the controls. Treatment with 500 ppm CoQ10 furthermore decreased the number of sialomucin-producing ACF and MDF per colon to 42% and 38% of the carcinogen control value without CoQ10, respectively. These results suggest that CoQ10 may be an effective chemopreventive agent against colon carcinogenesis.

Asian Pac J Cancer Prev. 2006 Oct-Dec;7(4):599-603

### **SERUM CYTOKINE LEVELS OF INTERLEUKIN-1BETA, -6, -8, TUMOUR NECROSIS FACTOR-ALPHA AND VASCULAR ENDOTHELIAL GROWTH FACTOR IN BREAST CANCER PATIENTS TREATED WITH TAMOXIFEN AND SUPPLEMENTED WITH COENZYME Q(10), RIBOFLAVIN AND NIACIN.**

The prognostic significance of supplementing coenzyme Q(10) (CoQ(10)), riboflavin and niacin (CoRN) along with tamoxifen to breast cancer patients was evaluated by measuring the serum cytokine levels of interleukin (IL)-1beta, IL-6, IL-8, tumour necrosis factor alpha (TNF-alpha) and vascular endothelial growth factor. In the present study, 84 breast cancer patients were randomized to receive a daily supplement of CoQ(10) 100 mg, riboflavin 10 mg and niacin 50 mg, one dosage per day along with tamoxifen 10 mg twice a day. Serum cytokine levels were elevated in untreated breast cancer patients (Group II) and significantly reduced after tamoxifen therapy for more than 1 year (Group III). When group III breast cancer patients were supplemented with CoRN for 45 days (Group IV) and 90 days (Group V) along with tamoxifen, a significant reduction in cytokine levels were observed ( $P < 0.05$ ). Such a decrease in serum cytokine levels after CoRN supplementation in breast cancer patients may suggest good prognosis and efficacy of the treatment, and might even offer protection from metastases and recurrence of cancer.

Basic Clin Pharmacol Toxicol. 2007 Jun;100(6):387-91

### **EFFECT OF COENZYME Q10, RIBOFLAVIN AND NIACIN ON SERUM CEA AND CA 15-3 LEVELS IN BREAST CANCER PATIENTS UNDERGOING TAMOXIFEN THERAPY.**

In breast cancer patients, it is not the primary tumour, but its metastases at distant sites that are the main cause of death. Circulating breast cancer tumour markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 15-3 (CA 15-3) are reliable indicators of impending relapse, in which an increasing tumour marker level is associated with a very likelihood of developing recurrence. In the present study, 84 breast cancer patients were randomized to receive a daily supplement of 100 mg coenzyme Q10 (CoQ10), 10 mg riboflavin and 50 mg niacin (CoRN) one dosage per day along with 10 mg tamoxifen (TAM) twice a day. Serum CEA and CA 15-3 levels were elevated in untreated breast cancer patients (group II) and their tumour marker levels significantly reduced upon tamoxifen therapy for more than 1 year (group III). Group III patients supplemented with CoRN for 45 d (group IV) and 90 d (group V) along with tamoxifen significantly reduced CEA and CA 15-3 levels. This study suggests supplementing CoRN to breast cancer patients along with tamoxifen reduces the serum tumour marker level and thereby reduce the risk of cancer recurrence and metastases.

Biol Pharm Bull. 2007 Feb;30(2):367-70

### **CYTOKINE THERAPY IN ADVANCED MELANOMA.**

Patients with melanoma considered at high risk for recurrence or regional metastases often have to choose between adjuvant interferon therapy or enrolling in a clinical trial. High-dose interleukin-2 therapy has had limited success in producing durable responses in stage IV melanoma; this success has been offset by marked toxicity. High-dose interferon alpha therapy has consistently shown disease-free survival benefit in clinical trials but has marked toxicity. The overall survival benefit has been inconsistent and controversial. Treatment with granulocyte macrophage colony-stimulating factor has shown promise in early studies. Various cytokines have had some success in treating advanced stage melanoma but with marked toxicity. Cytokine therapy that is well-tolerated and consistently provides an overall survival benefit for high-risk melanoma patients has not been achieved. Cytokines will continue to have a role in therapy for advanced-stage melanoma, most likely in combination with other immunomodulatory therapy. The challenge is finding the right doses, frequency, combinations, and duration of treatment.

J Drugs Dermatol. 2007 Apr;6(4):374-8

# JOURNAL ABSTRACTS

## Cocoa Polyphenols

### **PLASMA LDL AND HDL CHOLESTEROL AND OXIDIZED LDL CONCENTRATIONS ARE ALTERED IN NORMO- AND HYPERCHOLESTEROLEMIC HUMANS AFTER INTAKE OF DIFFERENT LEVELS OF COCOA POWDER.**

Cocoa powder is rich in polyphenols, such as catechins and procyanidins, and has been shown in a variety of subject models to inhibit oxidized LDL and atherogenesis. Our study evaluated plasma LDL cholesterol and oxidized LDL concentrations following the intake of different levels of cocoa powder (13, 19.5, and 26 g/d) in normocholesterolemic and mildly hypercholesterolemic humans. In this comparative, double-blind study, we examined 160 subjects who ingested either cocoa powder containing low-polyphenolic compounds (placebo-cocoa group) or 3 levels of cocoa powder containing high-polyphenolic compounds (13, 19.5, and 26 g/d for low-, middle-, and high-cocoa groups, respectively) for 4 wk. The test powders were consumed as a beverage after the addition of hot water, twice each day. Blood samples were collected at baseline and 4 wk after intake of the test beverages for the measurement of plasma lipids. Plasma oxidized LDL concentrations decreased in the low-, middle-, and high-cocoa groups compared with baseline. A stratified analysis was performed on 131 subjects who had a LDL cholesterol concentrations of  $>$  or  $\geq$  3.23 mmol/L at baseline. In these subjects, plasma LDL cholesterol, oxidized LDL, and apo B concentrations decreased, and the plasma HDL cholesterol concentration increased, relative to baseline in the low-, middle-, and high-cocoa groups. The results suggest that polyphenolic substances derived from cocoa powder may contribute to a reduction in LDL cholesterol, an elevation in HDL cholesterol, and the suppression of oxidized LDL.

J Nutr. 2007 Jun;137(6):1436-41

### **MECHANISMS AND EFFECTS OF GREEN TEA ON CARDIOVASCULAR HEALTH.**

Green tea, rich in antioxidant and anti-inflammatory catechins, especially epigallocatechin gallate (EGCG), has been shown to reduce surrogate markers of atherosclerosis and lipid peroxidation, particularly LDL oxidation and malondialdehyde concentrations, in several in vitro, animal, and limited clinical studies. Epidemiological observations in Southeast Asian countries indicate an inverse correlation exists between habitual consumption of green tea beverages and the incidence of cardiovascular events. A few short-term clinical studies have reported its effects in attenuating biomarkers of oxidative stress and inflammation among smokers, and an ability to decrease postprandial lipemia in hypercholesterolemic subjects has also been suggested. However, further investigations are needed to confirm the potential role of green tea beverages and the safety of green tea supplements in reducing body fat, as well as other biomarkers of cardiovascular disease risks.

Nutr Rev. 2007 Aug;65(8 Pt 1):361-75

### **TEA POLYPHENOLS FOR HEALTH PROMOTION.**

People have been consuming brewed tea from the leaves of the *Camellia sinensis* plant for almost 50 centuries. Although health benefits have been attributed to tea, especially green tea consumption since the beginning of its history, scientific investigations of this beverage and its constituents have been underway for less than three decades. Currently, tea, in the form of green or black tea, next to water, is the most widely consumed beverage in the world. In vitro and animal studies provide strong evidence that polyphenols derived from tea may possess the bioactivity to affect the pathogenesis of several chronic diseases. Among all tea polyphenols, epigallocatechin-3-gallate has been shown to be responsible for much of the health promoting ability of green tea. Tea and tea preparations have been shown to inhibit tumorigenesis in a variety of animal models of carcinogenesis. However, with increasing interest in the health promoting properties of tea and a significant rise in scientific investigation, this review covers recent findings on the medicinal properties and health benefits of tea with special reference to cancer and cardiovascular diseases.

Life Sci. 2007 Jul 26;81(7):519-33

### **FLAVONOID INTAKE AND COGNITIVE DECLINE OVER A 10-YEAR PERIOD.**

In the PAQUID (Personnes Agées Quid) study, the authors prospectively examined flavonoid intake in relation to cognitive function and decline among subjects aged 65 years or older. A total of 1,640 subjects free from dementia at baseline in 1990 and with reliable dietary assessment were reexamined four times over a 10-year period. Cognitive functioning was assessed through three psychometric tests (Mini-Mental State Examination, Benton's Visual Retention Test, "Isaacs" Set Test) at each visit.

Information on flavonoid intake was collected at baseline. A linear mixed model was used to analyze the evolution of cognitive performance according to quartiles of flavonoid intake. After adjustment for age, sex, and educational level, flavonoid intake was associated with better cognitive performance at baseline ( $p = 0.019$ ) and with a better evolution of the performance over time ( $p = 0.046$ ). Subjects included in the two highest quartiles of flavonoid intake had better cognitive evolution than did subjects in the lowest quartile. After 10 years' follow-up, subjects with the lowest flavonoid intake had lost on average 2.1 points on the Mini-Mental State Examination, whereas subjects with the highest quartile had lost 1.2 points. This gradient persisted after adjustment for several other potential confounders. This study raises the possibility that dietary flavonoid intake is associated with better cognitive evolution.

Am J Epidemiol. 2007 Jun 15;165(12):1364-71

### **BETA-GLUCANS IN PROMOTING HEALTH: PREVENTION AGAINST MUTATION AND CANCER.**

The polysaccharides beta-glucans occur as a principal component of the cellular walls. Some microorganisms, such as yeast and mushrooms, and also cereals such as oats and barley, are of economic interest because they contain large amounts of beta-glucans. These substances stimulate the immune system, modulating humoral and cellular immunity, and thereby have beneficial effect in fighting infections (bacterial, viral, fungal and parasitic). Beta-Glucans also exhibit hypocholesterolemic and anticoagulant properties. Recently, they have been demonstrated to be anti-cytotoxic, antimutagenic and anti-tumorigenic, making them promising candidate as pharmacological promoters of health.

Mutat Res. 2007 Aug 3

### **THE INTAKE OF FLAVONOIDS AND CAROTID ATHEROSCLEROSIS: THE KUOPIO ISCHAEMIC HEART DISEASE RISK FACTOR STUDY.**

The role of flavonoids in CVD is still unclear. In this cross-sectional study we assessed the relation between the intakes of twenty-six flavonoids from five subclasses: flavonols, flavones, flavanones, flavan-3-ols and anthocyanidins, and the mean common carotid artery intima-media thickness (CCA-IMT). The study population consisted of 1380 middle-aged eastern Finnish men for whom the mean CCA-IMT examinations were carried out as a part of the prospective population-based Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD). The mean intake of flavonoids was 128.5 (sd 206.7) mg/d and the mean CCA-IMT was 0.78 (sd 0.17) mm. In the lowest quartile of total flavonoid intake the non-adjusted mean CCA-IMT was 0.79 (sd 0.19) mm, while the mean CCA-IMT was 0.76 (sd 0.15) in the highest quartile ( $P < 0.001$ ). After adjustment for age, variables related to CCA-IMT measurement, history of atherosclerosis, smoking, BMI, diabetes, systolic blood pressure, serum HDL- and LDL-cholesterol, VO<sub>2</sub> max, and intakes of alcohol, SFA, folate, vitamins C and E, the total flavonoid intake was inversely associated with the mean CCA-IMT ( $P = 0.018$ ). Out of different flavonoid subclasses, flavan-3-ols were inversely associated with CCA-IMT ( $P = 0.025$ ) after statistical adjustment. There was a trend for an inverse association between intake of flavonols and mean CCA-IMT ( $P = 0.055$ ). We conclude that high intake of flavonoids is associated with decreased carotid atherosclerosis in middle-aged Finnish men.

Br J Nutr. 2007 Oct;98(4):814-8

### **APPLE POLYPHENOLS INFLUENCE CHOLESTEROL METABOLISM IN HEALTHY SUBJECTS WITH RELATIVELY HIGH BODY MASS INDEX.**

We performed a randomized double-blind, placebo-controlled study on moderately obese male and female subjects (71 subjects) with a body mass index ranging from 23 to 30 to evaluate the efficacy of 12-week intake of polyphenols extracted from apples and hop bract (600 mg/day). We confirmed that 12-week ingestion of polyphenol-containing capsules significantly decreased total cholesterol and LDL-cholesterol levels. The effects of the apple polyphenol-containing capsules were more marked than those of the hop bract polyphenol-containing capsules. The visceral fat area and the level of adiponectin in the group administered apple polyphenols improved in comparison with the control group. Blood and physical examinations revealed no clinical problems, and no adverse reactions were observed during the ingestion period. These results demonstrate that apple polyphenols regulate fat metabolism in healthy subjects with relatively high body mass index.

J Oleo Sci. 2007;56(8):417-28

### **COMBINATION THERAPY OF STATIN WITH FLAVONOIDS RICH EXTRACT FROM CHOKEBERRY FRUITS ENHANCED REDUCTION IN CARDIOVASCULAR RISK MARKERS IN PATIENTS AFTER MYOCARDIAL INFARCTION (MI).**

Recent studies have shown, that chronic flavonoids treatment improves vascular function and cardiovascular remodeling by decreasing superoxide anion production as well as by increasing NO release from endothelial cells. A progressive decrease in systolic blood pressure and reduction of low-density lipoprotein oxidation (Ox-LDL) has also been reported. However, none of

these studies were done in patient with coronary artery disease treated with statins. This was a double-blind, placebo-controlled, parallel trial. Forty-four patients (11 women and 33 men, mean age 66 years) who survived myocardial infarction and have received statin therapy for at least 6 months (80% dose of 40 mg/day simvastatin) were included in the study. The subjects were randomised to receive either 3 x 85 mg/day of chokeberry flavonoid extract (*Aronia melanocarpa* E) or placebo for a period of 6 weeks. The study extract was a commercially-available (OTC) product of the following declared composition: anthocyanins (about 25%), polymeric procyanidines (about 50%) and phenolic acids (about 9%). Compared to placebo (ANOVA and Tukey's test), flavonoids significantly reduced serum 8-isoprostans ( $p < 0.000$ ) and Ox-LDL levels ( $p < 0.000$ ) (by 38 and 29%, respectively), as well as hsCRP ( $p < 0.007$ ) and MCP-1 ( $p < 0.001$ ) levels (by 23 and 29%, respectively). In addition, significant increase in adiponectin ( $p < 0.03$ ) levels and reduction in systolic and diastolic blood pressure by a mean average of 11 and 7.2 mmHg, respectively were found. **CONCLUSION:** In view of the fact that chokeberry flavonoids reduce the severity of inflammation, regardless of statins, they can be used clinically for secondary prevention of ischaemic heart disease.

Atherosclerosis. 2007 Oct;194(2):e179-84

### **ABSORPTION OF DIETARY CHOLESTEROL OXIDATION PRODUCTS AND THEIR DOWNSTREAM METABOLIC EFFECTS ARE REDUCED BY DIETARY APPLE POLYPHENOLS.**

Exogenous and endogenous cholesterol oxidation products (COPs) perturb various metabolic processes, and thereby they may induce various homeostasis-related disorders. Here, we observed that procyanidin-rich dietary apple polyphenol (APP) from unripe apples alleviates the perturbation of lipid metabolism by decreasing the exogenous COP levels in rats. Dietary COPs may be the greatest source of COPs found in the human body. Rats (4 weeks of age) were fed AIN-purified diets containing 0.3% COPs supplemented with 0.5 or 2.5% APP for 3 weeks. Dietary APP alleviated the growth inhibition action of the exogenous COPs. The modulations of the liver lipid profile by COPs remained unchanged. However, serum total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels increased following the intake of dietary APP. Further, dietary APP inhibited the increase in lipid peroxide levels in the liver and serum by COPs. The activity of hepatic Delta6 desaturase was lowered by dietary APP in a dose-dependent manner, although exogenous COPs generally increased the activity of this enzyme. In keeping with this observation, Delta6 desaturation indices in the phospholipids and cholesteryl esters of the liver and serum lipids were lower in the APP-fed groups than those in the control group. Dietary APP also promoted the excretion of exogenous COPs, cholesterol, and acidic steroids in feces. Therefore, the inhibition of intestinal absorption of COPs may partly contribute to the alleviation of the perturbation of lipid metabolism and lipid peroxidation levels. Thus, APP may be an important removal agent of exogenous toxic material such as COPs contained in processed or fast foods.

Lipids. 2007 Mar;42(2):151-61

### **PREVENTION OF BONE LOSS BY PHLORIDZIN, AN APPLE POLYPHENOL, IN OVARIECTOMIZED RATS UNDER INFLAMMATION CONDITIONS.**

Aging and sex hormones related changes lead to inflammatory and oxidant conditions, which are involved in the pathogenesis of osteoporosis. Recent studies have suggested that polyphenols may exert a protective effect in such conditions. We assessed the effect of phloridzin (Phlo), a flavonoid exclusively found in apple, on bone metabolism in ovariectomized (OVX) or sham-operated (SH) rats with and without inflammation. Six-month-old Wistar rats were allocated to two equal groups that received either a control diet or a diet supplemented with 0.25% Phlo for 80 days. Three weeks before necropsy, inflammation was induced by subcutaneous injection of talc in 10 animals of each group. At necropsy, ovariectomy decreased both total (T-BMD) and metaphyseal (M-BMD) femoral bone mineral density ( $P < 0.01$ ). Inflammation conditions, checked by an increase in the spleen weight and alpha1-acid glycoprotein concentration in OVX rats, exacerbated the decrease in T-BMD ( $\text{g}/\text{cm}^2$ ) (as well as M-BMD) observed in castrated animals ( $P < 0.05$ ). Daily Phlo intake prevented ovariectomy-induced bone loss in conditions of inflammation as shown by T-BMD and M-BMD ( $P < 0.05$ ). At the diaphyseal site, BMD was improved by Phlo in OVX rats with or without inflammation ( $P < 0.05$ ). These results could be explained by changes in bone remodeling as the increased urinary deoxypyridinoline excretion in OVX and OVXinf animals was prevented by the polyphenol-rich diet ( $P < 0.001$ ), while plasma osteocalcin concentration was similar in all experimental groups. In conclusion, Phlo consumption may provide protection against ovariectomy-induced osteopenia under inflammation conditions by improving inflammation markers and bone resorption.

Calcif Tissue Int. 2005 Nov;77(5):311-8

### **MODULATION OF OXIDATIVE CELL DAMAGE BY RECONSTITUTED MIXTURES OF PHENOLIC APPLE JUICE EXTRACTS IN HUMAN COLON CELL LINES.**

Diets rich in fruits and vegetables are associated with a lower risk of tumour induction in the intestine and other sites. Apple juice with high amounts of antioxidative phenolics might protect the intestine against reactive oxygen species-mediated cell damage. We investigated to which extent the preventive effectiveness of polyphenolic juice extracts is governed by the amounts of five major constituents (rutin, phloridzin, chlorogenic acid, caffeic acid and epicatechin). In human colon cell lines (Caco-2, HT29), reconstituted mixtures of these phenolics were investigated in comparison to the original juice extracts, originating from cider and

table apples. Parameters studied were (oxidative) DNA damage (Comet assay), cellular redox status (dichlorofluorescein assay) and Trolox equivalent antioxidant capacity (TEAC). The TEAC of the reconstituted mixtures was higher compared to the respective original extracts (4.7-7.3 mM vs. 3.6-4.2 mM Trolox). After 24 hour cell incubation, menadione-induced (oxidative) DNA damage was more effectively reduced by the reconstituted mixtures (1-100 microg/mL, 24 h), as compared to the original extracts. In contrast, the cellular ROS level was reduced to a rather similar extent by original extracts and reconstituted mixtures. The results lead to the conclusion that the selected constituents in their authentic proportions substantially account for the antioxidative effectiveness of phenolic apple juice extracts.

Mol Nutr Food Res. 2006 Apr;50(4-5):413-7

### **GREEN TEA POLYPHENOLS: BIOLOGY AND THERAPEUTIC IMPLICATIONS IN CANCER.**

Multiple lines of evidence, mostly from population-based studies, suggest that green tea consumption is associated with reduced risk of several human malignancies such as cancer and diabetes. Epigallocatechin-3-gallate (EGCG), a major polyphenol found in green tea, is a widely studied chemopreventive agent with potential anticancer activity. Green tea polyphenols inhibit angiogenesis and metastasis, and induce growth arrest and apoptosis through regulation of multiple signaling pathways. Specifically, EGCG regulates expression of VEGF, matrix metalloproteinases, uPA, IGF-1, EGFR, cell cycle regulatory proteins and inhibits NFk B, PI3-K/Akt, Ras/Raf/MAPK and AP-1 signaling pathways, thereby causing strong cancer chemopreventive effects. This review discusses the molecular mechanisms of green tea polyphenols and their therapeutic implications in cancer.

Front Biosci. 2007 Sep 1;12:4881-99

Resveratrol

**RESVERATROL PROLONGS LIFESPAN AND RETARDS THE ONSET OF AGE-RELATED MARKERS IN A SHORT-LIVED VERTEBRATE.**

Resveratrol, a natural phytoalexin found in grapes and red wine, increases longevity in the short-lived invertebrates *Caenorhabditis elegans* and *Drosophila* and exerts a variety of biological effects in vertebrates, including protection from ischemia and neurotoxicity. Its effects on vertebrate lifespan were not yet known. The relatively long lifespan of mice, which live at least 2.5 years, is a hurdle for life-long pharmacological trials. Here, the authors used the short-lived seasonal fish *Nothobranchius furzeri* with a maximum recorded lifespan of 13 weeks in captivity. Short lifespan in this species is not the result of spontaneous or targeted genetic mutations, but a natural trait correlated with the necessity to breed in an ephemeral habitat and tied with accelerated development and expression of ageing biomarkers at a cellular level. Resveratrol was added to the food starting in early adulthood and caused a dose-dependent increase of median and maximum lifespan. In addition, resveratrol delays the age-dependent decay of locomotor activity and cognitive performances and reduces the expression of neurofibrillary degeneration in the brain. These results demonstrate that food supplementation with resveratrol prolongs lifespan and retards the expression of age-dependent traits in a short-lived vertebrate.

Curr Biol. 2006 Feb 7;16(3):296-300

**RESVERATROL IMPROVES MITOCHONDRIAL FUNCTION AND PROTECTS AGAINST METABOLIC DISEASE BY ACTIVATING SIRT1 AND PGC-1ALPHA.**

Diminished mitochondrial oxidative phosphorylation and aerobic capacity are associated with reduced longevity. We tested whether resveratrol (RSV), which is known to extend lifespan, impacts mitochondrial function and metabolic homeostasis. Treatment of mice with RSV significantly increased their aerobic capacity, as evidenced by their increased running time and consumption of oxygen in muscle fibers. RSV's effects were associated with an induction of genes for oxidative phosphorylation and mitochondrial biogenesis and were largely explained by an RSV-mediated decrease in PGC-1alpha acetylation and an increase in PGC-1alpha activity. This mechanism is consistent with RSV being a known activator of the protein deacetylase, SIRT1, and by the lack of effect of RSV in SIRT1(-/-) MEFs. Importantly, RSV treatment protected mice against diet-induced obesity and insulin resistance. These pharmacological effects of RSV combined with the association of three Sirt1 SNPs and energy homeostasis in Finnish subjects implicates SIRT1 as a key regulator of energy and metabolic homeostasis.

Cell. 2006 Dec 15;127(6):1109-22

**RESVERATROL IMPROVES HEALTH AND SURVIVAL OF MICE ON A HIGH-CALORIE DIET.**

Resveratrol (3,5,4'-trihydroxystilbene) extends the lifespan of diverse species including *Saccharomyces cerevisiae*, *Caenorhabditis elegans* and *Drosophila melanogaster*. In these organisms, lifespan extension is dependent on Sir2, a conserved deacetylase proposed to underlie the beneficial effects of caloric restriction. Here we show that resveratrol shifts the physiology of middle-aged mice on a high-calorie diet towards that of mice on a standard diet and significantly increases their survival. Resveratrol produces changes associated with longer lifespan, including increased insulin sensitivity, reduced insulin-like growth factor-1 (IGF-I) levels, increased AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor-gamma coactivator 1alpha (PGC-1alpha) activity, increased mitochondrial number, and improved motor function. Parametric analysis of gene set enrichment revealed that resveratrol opposed the effects of the high-calorie diet in 144 out of 153 significantly altered pathways. These data show that improving general health in mammals using small molecules is an attainable goal, and point to new approaches for treating obesity-related disorders and diseases of aging.

Nature. 2006 Nov 16;444(7117):337-42

**RESVERATROL, BUT NOT EGCG, IN THE DIET SUPPRESSES DMBA-INDUCED MAMMARY CANCER IN RATS.**

Despite the advent of new and aggressive therapeutics, breast cancer remains a leading killer among women; hence there is a need for the prevention of this disease. Several naturally occurring polyphenols have received much attention for their health benefits, including anti-carcinogenic properties. Two of these are resveratrol, a component of red grapes, and epigallocatechin-3-gallate (EGCG), the major catechin found in green tea. In this study, we tested the hypothesis that these two polyphenols

protect against chemically-induced mammary cancer by modulating mammary gland architecture, cell proliferation, and apoptosis. Female Sprague-Dawley CD rats were exposed to either resveratrol (1 g/kg AIN-76A diet), EGCG (0.065% in the drinking water), or control diet (AIN-76A) for the entirety of their life starting at birth. At 50 days postpartum, rats were treated with 60 mg dimethylbenz[a]anthracene (DMBA)/kg body weight to induce mammary cancer. Resveratrol, but not EGCG, suppressed mammary carcinogenesis (fewer tumors per rat and longer tumor latency). Analysis of mammary whole mounts from 50-day-old rats revealed that resveratrol, but not EGCG, treatment resulted in more differentiated lobular structures. Bromodeoxyuridine (BrdU) incorporation studies showed that resveratrol treatment caused a significant reduction in proliferative cells in mammary terminal ductal structures at 50 days postpartum, making them less susceptible to carcinogen insult. The epithelial cells of terminal end buds in the mammary glands of resveratrol-treated rats also showed an increase in apoptotic cells compared to the control or EGCG-treated rats as measured by a DNA fragmentation assay. At the given doses, resveratrol treatment resulted in a serum resveratrol concentration of 2.00 microM, while treatment with EGCG resulted in a serum EGCG concentration of 31.06 nM. 17beta-Estradiol, progesterone, and prolactin concentrations in the serum were not significantly affected by resveratrol or EGCG. Neither polyphenol treatment resulted in toxicity as tested by alterations in body weights, diet and drink consumptions, and day to vaginal opening. We conclude that resveratrol in the diet can reduce susceptibility to mammary cancer, while EGCG in the drinking water at the dose used was not effective.

J Carcinog. 2006 May 15;5:15

### **RESVERATROL SUPPRESSES PROSTATE CANCER PROGRESSION IN TRANSGENIC MICE.**

Resveratrol, a natural polyphenolic phytochemical, has been reported to act as an antioxidant and provide anticancer activities. We hypothesized that resveratrol would exert a chemopreventive effect against prostate cancer via regulation of sex steroid receptor and growth factor signaling pathways. In the current study, Transgenic Adenocarcinoma Mouse Prostate males were fed resveratrol (625 mg resveratrol per kg AIN-76A diet) or phytoestrogen-free, control diet (AIN-76A) starting at 5 weeks of age. Mechanisms of action and histopathology studies were conducted at 12 and 28 weeks of age, respectively. Resveratrol in the diet significantly reduced the incidence of poorly differentiated prostatic adenocarcinoma by 7.7-fold. In the dorsolateral prostate, resveratrol significantly inhibited cell proliferation, increased androgen receptor, estrogen receptor-beta, and insulin-like growth factor-1 receptor, and significantly decreased insulin-like growth factor (IGF)-1 and phospho-extracellular regulating kinase 1 (phospho-ERK 1). In the ventral prostate, resveratrol significantly reduced cell proliferation and phospho-ERKs 1 and 2, but did not significantly alter insulin-like growth factor-1 receptor and IGF-1. Serum total testosterone, free testosterone, estradiol, dihydrotestosterone and sex hormone-binding globulin (SHBG) concentrations and Simian Virus-40 large T antigen expression in the prostate were not altered in resveratrol-treated mice. Total resveratrol concentration in the blood serum of 12-week-old mice treated for 3 weeks with 625 mg resveratrol per kg diet was 52 +/- 18 nM. The decrease in cell proliferation and the potent growth factor, IGF-1, the down-regulation of downstream effectors, phospho-ERKs 1 and 2 and the increase in the putative tumor suppressor, estrogen receptor-beta, provide a biochemical basis for resveratrol suppressing prostate cancer development.

Carcinogenesis. 2007 Sep;28(9):1946-53

### **PLANT FOODS AND HERBAL SOURCES OF RESVERATROL.**

Stillbenes, in particular trans-resveratrol and its glucoside, are widely reported to be beneficial to health, having been shown to possess antioxidative, anticarcinogenic, and antitumor properties. Major dietary sources include grapes, wine, peanuts, and soy; however, they can also be introduced into the diet through Itadori tea, which has long been used in Japan and China as a traditional herbal remedy for heart disease and strokes. Analysis of grapes, peanuts, and Itadori tea shows that they contain mainly trans-resveratrol glucoside. In contrast, red wines are primarily a source of the aglycones cis- and trans-resveratrol. While peanuts and grapes contain low levels of the stilbenes, Itadori tea and red wine both supply relatively high concentrations of resveratrol. For people who do not consume alcohol, Itadori tea may be a suitable substitute for red wine. However, further study on the potential biological effects of other endogenous compounds in Itadori tea is required and there is also a need for more information on the absorption and in vivo biomedical actions of free and conjugated resveratrol.

J Agric Food Chem. 2002 May 22;50(11):3337-40

### **ROLE OF RESVERATROL IN PREVENTION AND THERAPY OF CANCER: PRECLINICAL AND CLINICAL STUDIES.**

Resveratrol, trans-3,5,4'-trihydroxystilbene, was first isolated in 1940 as a constituent of the roots of white hellebore (*Veratrum grandiflorum* O. Loes), but has since been found in various plants, including grapes, berries and peanuts. Besides cardioprotective effects, resveratrol exhibits anticancer properties, as suggested by its ability to suppress proliferation of a wide variety of tumor cells, including lymphoid and myeloid cancers; multiple myeloma; cancers of the breast, prostate, stomach, colon, pancreas, and thyroid; melanoma; head and neck squamous cell carcinoma; ovarian carcinoma; and cervical carcinoma. The growth-inhibitory effects of resveratrol are mediated through cell-cycle arrest; upregulation of p21Cip1/WAF1, p53 and Bax; down-regulation of survivin, cyclin D1, cyclin E, Bcl-2, Bcl-xL and cIAPs; and activation of caspases. Resveratrol has been shown to suppress the activation of several transcription factors, including NF-kappaB, AP-1 and Egr-1; to inhibit protein kinases

including IkappaBalpha kinase, JNK, MAPK, Akt, PKC, PKD and casein kinase II; and to down-regulate products of genes such as COX-2, 5-LOX, VEGF, IL-1, IL-6, IL-8, AR and PSA. These activities account for the suppression of angiogenesis by this stilbene. Resveratrol also has been shown to potentiate the apoptotic effects of cytokines (e.g., TRAIL), chemotherapeutic agents and gamma-radiation. Pharmacokinetic studies revealed that the target organs of resveratrol are liver and kidney, where it is concentrated after absorption and is mainly converted to a sulfated form and a glucuronide conjugate. In vivo, resveratrol blocks the multistep process of carcinogenesis at various stages: it blocks carcinogen activation by inhibiting aryl hydrocarbon-induced CYP1A1 expression and activity, and suppresses tumor initiation, promotion and progression. Besides chemopreventive effects, resveratrol appears to exhibit therapeutic effects against cancer. Limited data in humans have revealed that resveratrol is pharmacologically quite safe. Currently, structural analogues of resveratrol with improved bioavailability are being pursued as potential therapeutic agents for cancer.

Anticancer Res. 2004 Sep-Oct;24(5A):2783-840

### **INHIBITION OF CARDIAC FIBROBLAST PROLIFERATION AND MYOFIBROBLAST DIFFERENTIATION BY RESVERATROL.**

Cardiac fibroblasts (CFs) regulate myocardial remodeling by proliferating, differentiating, and secreting extracellular matrix proteins. Prolonged activation of CFs leads to cardiac fibrosis and reduced myocardial contractile function. Resveratrol (RES) exhibits a number of cardioprotective properties; however, the possibility that this compound affects CF function has not been considered. The current study tests whether RES directly influences the growth and proliferation of CFs and differentiation to the hypersecretory myofibroblast phenotype. Pretreatment of CFs with RES (5-25 microM) inhibited basal and ANG II-induced extracellular signal-regulated kinase (ERK) 1/2 and ERK kinase activation. This inhibition by RES reduced basal proliferation and blocked ANG II-induced growth and proliferation of CFs in a concentration-dependent manner, as measured by [(3)H]leucine and [(3)H]thymidine incorporation, respectively. RES pretreatment attenuated ERK phosphorylation when CFs were stimulated with 0.2 nM epidermal growth factor (EGF), a concentration at which EGF-induced ERK activation over basal was similar to the phosphorylation induced by 100 nM ANG II. Akt phosphorylation in CFs was unaffected by treatment with either 100 nM ANG II or 25 microM RES. Pretreatment of CFs with RES also reduced both ANG II- and transforming growth factor-beta-induced CF differentiation to the myofibroblast phenotype, indicated by a reduction in alpha-smooth muscle actin expression and stress fiber organization in CFs. This study identifies RES as an anti-fibrotic agent in the myocardium by limiting CF proliferation and differentiation, two critical steps in the pathogenesis of cardiac fibrosis.

Am J Physiol Heart Circ Physiol. 2005 Mar;288(3):H1131-8

### **EFFECT OF RESVERATROL ON ANTIOXIDANT ENZYME ACTIVITIES IN THE BRAIN OF HEALTHY RAT.**

We have studied the effect of resveratrol on lipoperoxidation and antioxidant enzyme activity level in the brain of healthy rats. When intraperitoneally administered, resveratrol significantly and dose dependently decreased brain malondialdehyde level. Resveratrol also increased in a dose-dependent way brain superoxide dismutase, catalase and peroxidase activities. Optimal effect on antioxidant enzyme and lipoperoxidation products were obtained with resveratrol concentration of 12.5 mg/kg body wt. Native polyacrylamide gel electrophoresis analysis of antioxidant isoenzymes revealed that resveratrol up regulated at least two acidic superoxide dismutase isoforms called A(1) and A(2), two basic isoforms called B(1) and B(2). Resveratrol also up regulated two catalase isoforms and a broad peroxidase band corresponding to several isoforms. All these findings suggest that resveratrol is able to cross the blood brain barrier and exerts potent antioxidant features. Resveratrol also exerts neuroprotective properties by up regulating several detoxifying enzymes, most of which are iron proteins.

Neurochem Res. 2007 Jun;32(6):981-7

### **EFFECTS OF RESVERATROL ON SKELETAL MUSCLE IN ISCHEMIA-REPERFUSION INJURY.**

**BACKGROUND:** Resveratrol, a polyphenol found in grape and red wine, was previously shown to have free radical scavenging and antioxidant properties in various tissues. In this study, the effects of resveratrol were investigated in muscle tissue concerning the ischemia reperfusion (I/R) injury of rat hindlimb. **METHODS:** Arterial circulation of right hindlimbs of 24 Sprague-Dawley rats was ceased by a tourniquet applied for four hours (h). The tourniquet was released at the end of 4th hours and rats were divided into four groups of six rats. Then, extremity was reperfused for 4h in group I and for 8h in group II. Resveratrol in 0.5% ethyl alcohol was administered with a dose of 10 mg/kg in the treatment groups (group I and group II) intraperitoneally. Only 0.5% ethyl alcohol were administered in the control groups (group III and group IV) intraperitoneally. Gastrocnemius muscle was used for histological assessments and the anterior tibial muscle was used for measurement of malondialdehyde (MDA) levels. **RESULTS:** MN infiltration, edema, changes in diameters of muscle fibers and segmental necrosis were less prominent in rats treated with resveratrol compared with control groups ( $p < 0.05$ ). The MDA levels was significantly lower in treatment groups ( $p < 0.05$ ). **CONCLUSION:** The results suggest that resveratrol may protect the skeletal muscles against I/R injury with its potent antioxidant properties.

## **INHIBITORY MECHANISMS OF RESVERATROL IN PLATELET ACTIVATION: PIVOTAL ROLES OF P38 MAPK AND NO/CYCLIC GMP.**

Resveratrol has been reported to have antiplatelet activity; however, the detailed mechanisms have not yet been resolved. This study aimed to systematically examine the detailed mechanisms of resveratrol in the prevention of platelet activation in vitro and in vivo. Resveratrol (0.05-0.25 micromol/l) showed stronger inhibition of platelet aggregation stimulated by collagen (1 microg/ml) than other agonists. Resveratrol (0.15 and 0.25 micromol/l) inhibited collagen-induced platelet activation accompanied by  $[Ca^{+2}]_i$  mobilization, thromboxane A<sub>2</sub> (TxA<sub>2</sub>) formation, phosphoinositide breakdown, and protein kinase C (PKC) activation. Resveratrol markedly increased levels of NO/cyclic guanosine monophosphate (GMP), and cyclic GMP-induced vasodilator-stimulated phosphoprotein phosphorylation. Resveratrol markedly inhibited p38 mitogen-activated protein kinase (MAPK) but not Jun N-terminal kinase or extracellular signal-

regulated kinase-2 phosphorylation in washed platelets. Resveratrol-reduced hydroxyl radical (OH<sup>-</sup>) formation in the electron spin resonance study. In an in vivo study, resveratrol (5 mg/kg) significantly prolonged platelet plug formation of mice. In conclusion, the main findings of this study suggest that the inhibitory effects of resveratrol possibly involve (i) inhibition of the p38 MAPK-cytosolic phospholipase A<sub>2</sub>-arachidonic acid-TxA<sub>2</sub>- $[Ca^{+2}]_i$  cascade and (ii) activation of NO/cyclic GMP, resulting in inhibition of phospholipase C and/or PKC activation. Resveratrol is likely to exert significant protective effects in thromboembolic-related disorders by inhibiting platelet aggregation.

Br J Haematol. 2007 Nov;139(3):475-85

## Blueberries

**ANTHOCYANINS IN WILD BLUEBERRIES OF QUEBEC: EXTRACTION AND IDENTIFICATION.**

Anthocyanins were extracted from a mixture of berries of *Vaccinium angustifolium* and *Vaccinium myrtilloides* at 7.7 degrees C, 26 degrees C, and 79 degrees C using ethanol alone or ethanol acidified with hydrochloric, citric, tartaric, lactic, or phosphoric acids at a solvent to solid ratio of 10. The effect of these parameters on extracted anthocyanins stability was investigated. The pH-differential and HPLC-DAD methods were used to determine anthocyanin contents. Extracted anthocyanins were purified on a C-18 solid-phase extraction cartridge and characterized by HPLC/electrospray ionization/mass spectrometry (HPLC-ESI-MS/MS). Anthocyanins were identified according to their HPLC retention times, elution order, and MS fragmentation pattern and by comparison with standards and published data. Anthocyanin extractions gave different yields depending on the type of added acid and the extraction temperature. High yields of monomeric and total anthocyanins (26.3 and 28.9 mg/g of dry matter) were obtained at 79 degrees C using phosphoric acid. Extraction using tartaric acid at 79 degrees C provided the lowest degradation index (1.05). Anthocyanins were stable and browning by polyphenol oxidase was inhibited under these conditions. Of the six common anthocyanindins, five were identified in the extracts, namely, delphinidin, cyanidin, peonidin, petunidin, and malvidin; pelargonidin was not found. In addition to well-known major anthocyanins, new anthocyanins were identified for the first time in extracts of wild blueberries from Quebec.

J Agric Food Chem. 2007 Jul 11;55(14):5626-35

**EFFECT OF ANTHOCYANIN FRACTIONS FROM SELECTED CULTIVARS OF GEORGIA-GROWN BLUEBERRIES ON APOPTOSIS AND PHASE II ENZYMES.**

In recent years, considerable attention has been paid to anthocyanins due to their abilities to inhibit oxidative stress and cell proliferation. The regulations of apoptosis and the phase II enzymes glutathione-S-transferase (GST) and quinone reductase (QR) are other potential mechanisms through which flavonoids such as anthocyanins may prevent cancer. Our study confirmed that anthocyanin fractions from high bush blueberry cultivars increased apoptosis using two different methods: DNA fragmentation and caspase-3 activity. The effect of anthocyanins on the activity of the detoxifying enzymes GST and QR was also determined. Major anthocyanins identified were delphinidin, cyanidin, peonidin, petunidin, and malvidin. In Tifblue and Powderblue cultivars, DNA fragmentation increased at anthocyanin concentrations from 50 to 150 microg/mL, but cells treated with the anthocyanin fraction of Brightblue and Brightwell showed a prominent ladder at 50-100 microg/mL when compared to cells treated with 150 microg/mL. There was a significant difference in the caspase-3 activity ( $P < 0.05$ ) between the control cells and the cells treated with anthocyanins from all of the cultivars. The response correlated positively with dose. The QR activity was lower in all cells treated with an anthocyanin fraction from Tifblue, Powderblue, Brightblue, and Brightwell cultivars than in control cells ( $P < 0.05$ ). The activity decreased gradually when treated with increased concentrations of anthocyanin fractions (50-150 microg/mL) in the Tifblue and Powderblue cultivars. The GST activity was lower ( $P < 0.05$ ) in cells treated with anthocyanin fractions from all of the cultivars and at all concentrations. These results indicated that apoptosis was confirmed in HT-29 cells when treated with anthocyanins from blueberry cultivars at 50-150 microg/mL concentrations, but these same concentrations decrease QR and GST activities rather than induce them.

J Agric Food Chem. 2007 Apr 18;55(8):3180-5

**INHIBITION OF CANCER CELL PROLIFERATION AND SUPPRESSION OF TNF-INDUCED ACTIVATION OF NFKAPPAB BY EDIBLE BERRY JUICE.**

**BACKGROUND:** Berries contain several phytochemicals, such as phenolic acids, proanthocyanidins, anthocyanins and other flavonoids. There has been growing interest in a variety of potential chemopreventive activities of edible berries. The potential chemopreventive activity of a variety of small berries cultivated or collected in the province of Québec, Canada were evaluated here. **MATERIALS AND METHODS:** Strawberry, raspberry, black currant, red currant, white currant, gooseberry, high-bush blueberry, low-bush blueberry, velvet leaf blueberry, serviceberry, blackberry, black chokeberry, sea buckthorn and cranberry were evaluated for antioxidant capacity, anti-proliferative activity, anti-inflammatory activity, induction of apoptosis and cell cycle arrest. **RESULTS:** The growth of various cancer cell lines, including those of stomach, prostate, intestine and breast, was strongly inhibited by raspberry, black currant, white currant, gooseberry, velvet leaf blueberry, low-bush blueberry, sea buckthorn and cranberry juice, but not (or only slightly) by strawberry, high-bush blueberry, serviceberry, red currant, or blackberry juice. No correlation was found between the anti-proliferative activity of berry juices and their antioxidant capacity ( $p > 0.05$ ). The inhibition

of cancer cell proliferation by berry juices did not involve caspase-dependent apoptosis, but appeared to involve cell-cycle arrest, as evidenced by down-regulation of the expression of cdk4, cdk6, cyclin D1 and cyclin D3. Of the 13 berries tested, juice of 6 significantly inhibited the TNF-induced activation of COX-2 expression and activation of the nuclear transcription factor NFkappaB. CONCLUSION: These results illustrate that berry juices have striking differences in their potential chemopreventive activity and that the inclusion of a variety of berries in the diet might be useful for preventing the development of tumors.

Anticancer Res. 2007 Mar-Apr;27(2):937-48

### **DIFFERENTIAL INHIBITION OF UV-INDUCED ACTIVATION OF NF KAPPA B AND AP-1 BY EXTRACTS FROM BLACK RASPBERRIES, STRAWBERRIES, AND BLUEBERRIES.**

Recent studies have shown that the transactivation of nuclear factor kappa B (NF kappa B) and activator protein-1 (AP-1) plays an important mechanistic role in ultraviolet (UV)-induced skin carcinogenesis in mice. We also demonstrated that a methanol extract (ME) fraction from black raspberries (*Rubus occidentalis*) (RO; RO-ME) inhibits benzo[a]pyrene-7,8-diol-9,10-epoxide [B(a)PDE]-induced activation of NF kappa B and AP-1 in cultured mouse epidermal cells. We determined if RO-ME might also inhibit the induction of NF kappa B and AP-1 in mouse epidermal cells exposed to mid UV radiation (UVB) and short UV radiation (UVC) and whether methanol fractions from strawberries and blueberries would also be effective. Our results showed that RO-ME inhibited UVB-induced activation of NF kappa B in mouse epidermal cells in a time- and dose-dependent manner; however, the methanol fractions from strawberries and blueberries were ineffective. Interestingly, none of the fractions from all 3 berry types inhibited UVB- or UVC-induced activation of AP-1, suggesting that inhibition of UV-induced signaling pathways is specific for black raspberries and NF kappa B. Cyanidin-3-rutinoside, an anthocyanin found in abundance in black raspberries and not in strawberries or high-bush blueberries, was found to contribute to the inhibition of UVB-induced activation of NF kappa B. These results suggest that berries differ in their ability to influence signaling pathways leading to activation of NF kappa B and AP-1 when using UV light as the inducer.

Nutr Cancer. 2007;58(2):205-12

### **CRANBERRY AND BLUEBERRY: EVIDENCE FOR PROTECTIVE EFFECTS AGAINST CANCER AND VASCULAR DISEASES.**

Growing evidence from tissue culture, animal, and clinical models suggests that the flavonoid-rich fruits of the North American cranberry and blueberry (*Vaccinium* spp.) have the potential ability to limit the development and severity of certain cancers and vascular diseases including atherosclerosis, ischemic stroke, and neurodegenerative diseases of aging. The fruits contain a variety of phytochemicals that could contribute to these protective effects, including flavonoids such as anthocyanins, flavonols, and proanthocyanidins; substituted cinnamic acids and stilbenes; and triterpenoids such as ursolic acid and its esters. Cranberry and blueberry constituents are likely to act by mechanisms that counteract oxidative stress, decrease inflammation, and modulate macromolecular interactions and expression of genes associated with disease processes. The evidence suggests a potential role for dietary cranberry and blueberry in the prevention of cancer and vascular diseases, justifying further research to determine how the bioavailability and metabolism of berry phytonutrients influence their activity in vivo.

Mol Nutr Food Res. 2007 Jun;51(6):652-64

### **ANTI-INFLAMMATORY AND ANTINOCICEPTIVE PROPERTIES OF BLUEBERRY EXTRACT (*VACCINIUM CORYMBOSUM*).**

Blueberries are among the edible fruits that are recognized best for their potential health benefits. The crude extract from *Vaccinium corymbosum* was assessed in anti-inflammatory and antinociceptive models. The crude hydroalcoholic extract was administered orally at doses of 100, 200 or 300 mg kg<sup>-1</sup> for all the assays. In the carrageenan test, the crude extract reduced rat paw oedema by 9.8, 28.5 and 65.9%, respectively. For the histamine assay, the reductions of oedema were 70.1, 71.7 and 81.9%, respectively. In the myeloperoxidase (MPO) assay, 300 mg kg<sup>-1</sup> crude extract produced a significant inhibition of the MPO activity, at 6 h and 24 h after injection of carrageenan, by 42.8 and 46.2%, respectively. With the granulomatous tissue assay dexamethasone displayed significant activity, whereas the blueberry extract was inactive. For the abdominal constriction test, inhibitions of 49.0, 54.5, 53.5%, respectively, were observed for the crude extract, and 61.4% for indometacin. In the formalin test, the crude extract (200 and 300 mg kg<sup>-1</sup>) and indometacin inhibited only the second phase by 36.2, 35.3 and 45.8%, respectively. Considering that the crude extract of blueberry displayed antinociceptive and anti-inflammatory activity, its consumption may be helpful for the treatment of inflammatory disorders.

J Pharm Pharmacol. 2007 Apr;59(4):591-6

### **FRUIT POLYPHENOLS AND THEIR EFFECTS ON NEURONAL SIGNALING AND BEHAVIOR IN SENESCENCE.**

The onset of age-related neurodegenerative diseases superimposed on a declining nervous system could exacerbate the motor

and cognitive behavioral deficits that normally occur in senescence. It is likely that, in cases of severe deficits in memory or motor function, hospitalization and/or custodial care would be a likely outcome. This means that unless some way is found to reduce these age-related decrements in neuronal function, healthcare costs will continue to rise exponentially. Thus, it is extremely important to explore methods to retard or reverse the age-related neuronal deficits as well as their subsequent, behavioral manifestations. Applying molecular biological approaches to slow aging in the human condition may be years away. So it is important to determine what methods can be used today to increase healthy aging, forestall the onset of these diseases, and create conditions favorable to obtaining a "longevity dividend" in both financial and human terms. In this regard, epidemiological studies indicate that consumption of diets rich in antioxidants and anti-inflammatory compounds, such as those found in fruits and vegetables, may lower the risk of developing age-related neurodegenerative diseases, such as Alzheimer's or Parkinson's diseases (AD and PD). Research suggests that the polyphenolic compounds found in fruits, such as blueberries, may exert their beneficial effects by altering stress signaling and neuronal communication, suggesting that interventions may exert protection against age-related deficits in cognitive and motor function. The purpose of this article is to discuss the benefits of these interventions in rodent models and to describe the putative molecular mechanisms involved in their benefits.

Ann N Y Acad Sci. 2007 Apr;1100:470-85

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