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*Journal*  
**ABSTRACTS****Viscous Soluble Fiber*****Carbohydrates and dietary fiber.***

The most widely spread eating habit is characterized by a reduced intake of dietary fiber, an increased intake of simple sugars, a high intake of refined grain products, an altered fat composition of the diet, and a dietary pattern characterized by a high glycemic load, an increased body weight and reduced physical activity. In this chapter the effects of this eating pattern on disease risk will be outlined. There are no epidemiological studies showing that the increase of glucose, fructose or sucrose intake is directly and independently associated with an increased risk of atherosclerosis or coronary heart disease (CHD). On the other hand a large number of studies has reported a reduction of fatal and non-fatal CHD events as a function of the intake of complex carbohydrates—respectively ‘dietary fiber’ or selected fiber-rich food (e.g., whole grain cereals). It seems that eating too much ‘fast’ carbohydrate [i.e., carbohydrates with a high glycemic index (GI)] may have deleterious long-term consequences. Indeed the last decades have shown that a low fat (and consecutively high carbohydrate) diet alone is not the best strategy to combat modern diseases including atherosclerosis. Quantity and quality issues in carbohydrate nutrient content are as important as they are for fat. Multiple lines of evidence suggest that for cardiovascular disease prevention a high sugar intake should be avoided. There is growing evidence of the high impact of dietary fiber and foods with a low GI on single risk factors (e.g., lipid pattern, diabetes, inflammation, endothelial function etc.) as well as also the development of the endpoints of atherosclerosis especially CHD.

Handb Exp Pharmacol. 2005;(170):231-61

**LOW-INSULIN-RESPONSE DIETS MAY DECREASE PLASMA C-REACTIVE PROTEIN BY INFLUENCING ADIPOCYTE FUNCTION.**

Hepatic production of many acute phase reactants, including C-reactive protein (CRP), is induced primarily by interleukin-6 (IL-6). A significant fraction of the plasma pool of IL-6 derives from adipocytes. Physiological concentrations of insulin as well as of catecholamines have been shown to boost adipocyte production of IL-6 dose-dependently. High fasting and postprandial insulin levels can increase adipocyte exposure to catecholamines by activating the sympathetic nervous system, as well as by provoking postabsorptive hypoglycemia that triggers adrenal secretion of epinephrine. It follows that diets which promote low diurnal insulin levels - by minimizing the stimulus to postprandial insulin release, and by aiding muscle insulin sensitivity - should be associated with lower CRP levels. In fact, recent epidemiology demonstrates a correlation between dietary glycemic load and serum CRP in women, and a recent clinical study reports a 28% reduction in serum CRP following adoption of a whole-food vegan diet rich in soluble fiber. Whether very-low-fat diets which promote insulin sensitivity - and thus down-regulate insulin secretion - can influence CRP, remains to be seen. These considerations suggest that it may be possible to achieve worthwhile reductions in CRP by avoiding high-insulin-response starchy foods and by ingesting more soluble fiber, in foods or as a meal-time supplement.

Med Hypotheses. 2005;64(2):385-7

**CONCENTRATED OAT BETA-GLUCAN, A FERMENTABLE FIBER, LOWERS SERUM CHOLESTEROL IN HYPERCHOLESTEROLEMIC ADULTS IN A RANDOMIZED CONTROLLED TRIAL.**

**BACKGROUND:** Soluble fibers lower serum lipids, but are difficult to incorporate into products acceptable to consumers. We investigated the physiological effects of a concentrated oat beta-glucan on cardiovascular disease (CVD) endpoints in human subjects. We also compared the fermentability of concentrated oat beta-glucan with inulin and guar gum in a model intestinal fermentation system. **METHODS:** Seventy-five hypercholesterolemic men and women were randomly assigned to one of two treatments: 6 grams/day concentrated oat beta-glucan or 6 grams/day dextrose (control). Fasting blood samples were collected at baseline, week 3, and week 6 and analyzed for total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, glucose, insulin, homocysteine and C-reactive protein (CRP). To estimate colonic fermentability, 0.5 g concentrated oat beta-glucan was incubated in a batch model intestinal fermentation system, using human fecal inoculum to provide representative microflora. Fecal donors were not involved with the beta-glucan feeding trial. Inulin and guar gum were also incubated in separate serum bottles for comparison. **RESULTS:** Oat beta-glucan produced significant reduction from baseline in total cholesterol (-0.3 +/- 0.1

mmol/L) and LDL cholesterol (-0.3 +/- 0.1 mmol/L), and the reduction in LDL cholesterol were significantly greater than in the control group ( $p = 0.03$ ). Concentrated oat beta-glucan was a fermentable fiber and produced total SCFA and acetate concentrations similar to inulin and guar gum. Concentrated oat beta-glucan produced the highest concentrations of butyrate at 4, 8, and 12 hours. **CONCLUSION:** Six grams concentrated oat beta-glucan per day for six weeks significantly reduced total and LDL cholesterol in subjects with elevated cholesterol, and the LDL cholesterol reduction was greater than the change in the control group. Based on a model intestinal fermentation, this oat beta-glucan was fermentable, producing higher amounts of butyrate than other fibers. Thus, a practical dose of beta-glucan can significantly lower serum lipids in a high-risk population and may improve colon health.

Nutr J. 2007 Mar 26;6:6

### **SUPPLEMENTATION OF A HIGH-CARBOHYDRATE BREAKFAST WITH BARLEY BETA-GLUCAN IMPROVES POSTPRANDIAL GLYCAEMIC RESPONSE FOR MEALS BUT NOT BEVERAGES.**

There is growing support for the protective role of soluble fibre in type II diabetes. Soluble fibre beta-glucan found in cereal products including oats and barley may be the active component. There is evidence of postprandial blunting of blood glucose and insulin responses to dietary carbohydrates when oat soluble fibre is supplemented into the diet but few trials have been carried out using natural barley or enriched barley beta-glucan products. The aim of this trial was to investigate the postprandial effect of a highly enriched barley beta-glucan product on blood glucose, insulin and lipids when given with a high-CHO food and a high-CHO drink. 18 lean, healthy men completed a 4 treatment intervention trial comprising (i) high-CHO(food control), (ii) high-CHO (food+fibre), (iii) high-CHO(drink control), (iv) high-CHO(drink+fibre) where a 10g dose of barley beta-glucan fibre supplement (Cerogen) containing 6.31g beta-glucan was added to food and drink controls. There was an increase of glucose and insulin following all 4 treatments. Addition of the beta-glucan supplement significantly blunted the glycaemic and insulinaemic responses on the food ( $p < 0.05$ ) but not drink ( $p > 0.05$ ) treatments when compared to controls. The high-CHO breakfasts decreased total, LDL- and HDL-cholesterol from baseline to 60 mins postprandially but there were no differential effects of beta-glucan treatment on circulating lipids. We conclude that a high dose barley beta-glucan supplement can improve glucose control when added to a high-CHO starchy food, probably due to increased gastro-intestinal viscosity, but not when added to a high-CHO beverage where rapid absorption combined with decreased beta-glucan concentration and viscosity may obviate this mechanism.

Asia Pac J Clin Nutr. 2007;16(1):16-24

### **CHANGES IN SERUM LIPIDS AND POSTPRANDIAL GLUCOSE AND INSULIN CONCENTRATIONS AFTER CONSUMPTION OF BEVERAGES WITH BETA-GLUCANS FROM OATS OR BARLEY: A RANDOMISED DOSE-CONTROLLED TRIAL.**

**OBJECTIVES:** To investigate side by side the effects on serum lipoproteins and postprandial glucose and insulin concentrations of beverages enriched with 5 or 10 g of beta-glucans from oats or barley. **DESIGN AND SETTING:** An 8-week single blind, controlled study with five parallel groups carried out at two centres under identical conditions. **SUBJECTS:** A total of 100 free-living hypercholesterolaemic subjects were recruited locally and 89 completed the study. **INTERVENTIONS:** During a 3-week run-in period all subjects consumed a control beverage. For the following 5-week period four groups received a beverage with 5 or 10 g beta-glucans from oats or barley and one group continued with the control beverage. Blood samples in weeks 0, 2, 3, 7 and 8 were analysed for serum lipids, lipoproteins, glucose and insulin. Postprandial concentrations of glucose and insulin were compared between control and the beverage with 5 g of beta-glucans from oats or barley. **RESULTS:** Compared to control, 5 g of beta-glucans from oats significantly lowered total-cholesterol by 7.4% ( $P < 0.01$ ), and postprandial concentrations of glucose (30 min,  $P = 0.005$ ) and insulin (30 min,  $P = 0.025$ ). The beverage with 10 g of beta-glucans from oats did not affect serum lipids significantly in comparison with control. No statistically significant effects compared to control of the beverages with barley beta-glucans were found. **CONCLUSIONS:** A daily consumption of 5 g of oat beta-glucans in a beverage improved the lipid and glucose metabolism, while barley beta-glucans did not.

Eur J Clin Nutr. 2005 Nov;59(11):1272-81

### **CONSUMPTION OF BOTH RESISTANT STARCH AND BETA-GLUCAN IMPROVES POSTPRANDIAL PLASMA GLUCOSE AND INSULIN IN WOMEN.**

**OBJECTIVE:** Consumption of a meal high in resistant starch or soluble fiber (beta-glucan) decreases peak insulin and glucose concentrations and areas under the curve (AUCs). The objective was to determine whether the effects of soluble fiber and resistant starch on glycemic variables are additive. **RESEARCH DESIGN AND METHODS:** Ten normal-weight (43.5 years of age, BMI 22.0 kg/m<sup>2</sup>) and 10 overweight women (43.3 years of age, BMI 30.4 kg/m<sup>2</sup>) consumed 10 tolerance meals in a Latin square design. Meals (1 g carbohydrate/kg body wt) were glucose alone or muffins made with different levels of soluble fiber (0.26, 0.68, or 2.3 g beta-glucan/100 g muffin) and three levels of resistant starch (0.71, 2.57, or 5.06 g/100 g muffin). **RESULTS:** Overweight subjects had plasma insulin concentrations higher than those of normal-weight subjects but maintained similar plasma glucose levels. Compared with low beta-glucan-low resistant starch muffins, glucose and insulin AUC decreased when beta-glucan (17

and 33%, respectively) or resistant starch (24 and 38%, respectively) content was increased. The greatest AUC reduction occurred after meals containing both high beta-glucan-high resistant starch (33 and 59% lower AUC for glucose and insulin, respectively). Overweight women were somewhat more insulin resistant than control women. **CONCLUSIONS:** Soluble fiber appears to have a greater effect on postprandial insulin response while glucose reduction is greater after resistant starch from high-amylose cornstarch. The reduction in glycemic response was enhanced by combining resistant starch and soluble fiber. Consumption of foods containing moderate amounts of these fibers may improve glucose metabolism in both normal and overweight women.

Diabetes Care. 2006 May;29(5):976-81

### **OAT-DERIVED BETA-GLUCAN SIGNIFICANTLY IMPROVES HDLC AND DIMINISHES LDLC AND NON-HDL CHOLESTEROL IN OVERWEIGHT INDIVIDUALS WITH MILD HYPERCHOLESTEROLEMIA.**

**OBJECTIVE:** To investigate the effect of bread formulated with 6 g of beta-glucan (oat soluble fiber) on serum lipids in overweight normotensive subjects with mild to moderate hypercholesterolemia. **DESIGN:** Thirty-eight male subjects [mean age 59.8 +/- 0.6 yr, mean body mass index (BMI) 28.3 +/- 0.6 kg/m(2)] who were eligible for the study ate an isocaloric diet for a 1-week period. They were then divided into 2 groups: group A (n = 19), who were maintained on American Heart Association (AHA) Step II diet, including whole wheat bread, and group B (n = 19), who were maintained on AHA Step II diet containing high levels of monounsaturated fatty acids plus bread containing 6 g of beta-glucan (Nutrim-OB) for 8 weeks. Plasma lipids and glucose were measured at baseline and after weeks 8 in all subjects. All subjects were advised to walk for 60 minutes every day. **RESULTS:** There was a significant increase (upward arrow 27.8%) in plasma high density lipoprotein (HDL) cholesterol in the beta-glucan group (group A) from 39.4 +/- 2.0 to 49.5 +/- 2.1 mg/dL (P < 0.001), but there was no change in group B. There was a significant reduction in total cholesterol in the 2 groups to approximately the same extent: group A, from 232.8 +/- 2.7 mg/dL to 202.7 +/- 6.7 mg/dL; P < 0.001; and group B, from 231.8 +/- 4.3 mg/dL to 194.2 +/- 4.3 mg dL; P < 0.001. Plasma low density lipoprotein (LDL) cholesterol also decreased significantly in the two groups: group A, from 160.3 +/- 2.8 mg/dL to 133.2 +/- 5.4 mg/dL; P < 0.001; group B, from 167.9 +/- 4.3 mg/dL to 120.9 +/- 4.3 mg/dL; P < 0.001; however, the beta-glucan fortified diet was significantly more effective (downward arrow 27.3% vs. downward arrow 16.8%; P < 0.04). There was a small and insignificant reduction in plasma very LDL (VLDL) cholesterol and triglycerides in the two groups. Similarly, non-HDL cholesterol levels were also decreased, with beta-glucan diet producing significantly higher effect (downward arrow 24.5% vs. downward arrow 16.1%; P < 0.04). The beta-glucan diet also produced higher reduction in total cholesterol/HDL cholesterol ratio (downward arrow 33.3% vs. downward arrow 8.4%; P < 0.003) and LDL cholesterol/HDL cholesterol ratio (downward arrow 42.1% vs. downward arrow 13.3%; P < 0.001) than the diet without beta-glucan. The beta-glucan diet also decreased fasting plasma glucose (P < 0.4), whereas the other diet had no effect. Interestingly, both diets reduced body weight and BMI significantly, with beta-glucan diet having a greater effect. **CONCLUSIONS:** Six grams of beta-glucan from oats added to the AHA Step II diet and moderate physical activity improved lipid profile and caused a decrease in weight and, thus, reduced the risk of cardiovascular events in overweight male individuals with mild to moderate hypercholesterolemia. The diet with added beta-glucan was well accepted and tolerated.

Am J Ther. 2007 Mar-Apr;14(2):203-12

### **DIET AND LIFESTYLE RECOMMENDATIONS REVISION 2006: A SCIENTIFIC STATEMENT FROM THE AMERICAN HEART ASSOCIATION NUTRITION COMMITTEE.**

Improving diet and lifestyle is a critical component of the American Heart Association's strategy for cardiovascular disease risk reduction in the general population. This document presents recommendations designed to meet this objective. Specific goals are to consume an overall healthy diet; aim for a healthy body weight; aim for recommended levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides; aim for normal blood pressure; aim for a normal blood glucose level; be physically active; and avoid use of and exposure to tobacco products. The recommendations are to balance caloric intake and physical activity to achieve and maintain a healthy body weight; consume a diet rich in vegetables and fruits; choose whole-grain, high-fiber foods; consume fish, especially oily fish, at least twice a week; limit intake of saturated fat to <7% of energy, trans fat to <1% of energy, and cholesterol to <300 mg/day by choosing lean meats and vegetable alternatives, fat-free (skim) or low-fat (1% fat) dairy products and minimize intake of partially hydrogenated fats; minimize intake of beverages and foods with added sugars; choose and prepare foods with little or no salt; if you consume alcohol, do so in moderation; and when you eat food prepared outside of the home, follow these Diet and Lifestyle Recommendations. By adhering to these diet and lifestyle recommendations, Americans can substantially reduce their risk of developing cardiovascular disease, which remains the leading cause of morbidity and mortality in the United States.

Circulation. 2006 Jul 4;114(1):82-96

### **DIETARY FIBRE AND RISK OF BREAST CANCER IN THE UK WOMEN'S COHORT STUDY.**

**BACKGROUND:** Reports of relationships between dietary fibre intake and breast cancer have been inconsistent. Previous cohort studies have been limited by a narrow range of intakes. **METHODS:** Women who developed invasive breast cancer, 350 post-

menopausally and 257 pre-menopausally, during 240 959 person-years of follow-up in the UK Women's Cohort Study (UKWCS) were studied. This cohort has 35 792 subjects with a wide range of exposure to dietary fibre with intakes of total fibre in the lowest quintile of <20 g/day up to >30 g/day in the top quintile. Fibre and breast cancer relationships were explored using Cox regression modelling adjusted for measurement error. Effects of fibre, adjusting for confounders were examined for pre- and post-menopausal women separately. RESULTS: In pre-menopausal, but not post-menopausal women a statistically significant inverse relationship was found between total fibre intake and risk of breast cancer (P for trend = 0.01). The top quintile of fibre intake was associated with a hazard ratio of 0.48 [95% confidence interval (CI) 0.24-0.96] compared with the lowest quintile. Pre-menopausally, fibre from cereals was inversely associated with risk of breast cancer (P for trend = 0.05) and fibre from fruit had a borderline inverse relationship (P for trend = 0.09). A further model including dietary folate strengthened the significance of the inverse relationship between total fibre and pre-menopausal breast cancer. CONCLUSIONS: These findings suggest that in pre-menopausal women, total fibre is protective against breast cancer; in particular, fibre from cereals and possibly fruit.

Int J Epidemiol. 2007 Jan 24

### **EFFECTS OF MODERATE EXERCISE AND OAT BETA-GLUCAN ON LUNG TUMOR METASTASES AND MACROPHAGE ANTITUMOR CYTOTOXICITY.**

Both moderate exercise and the soluble fiber beta-glucan can have beneficial effects on the initiation and growth of tumors, but the data are limited, and there is no information on their combined effects. This study tested the independent and combined effects of short-term moderate-exercise training and the soluble oat fiber beta-glucan (ObetaG) on the metastatic spread of injected tumor cells and macrophage antitumor cytotoxicity. Male C57BL/6 mice were assigned to one of four groups: exercise (Ex)-H<sub>2</sub>O, Ex-ObetaG, control (Con)-H<sub>2</sub>O, or Con-ObetaG. ObetaG was fed in the drinking water for 10 days before tumor administration and death. Exercise consisted of treadmill running (1 h/day) for 6 days. After rest or exercise on the last day of training, syngeneic B16 melanoma cells (2 x 10<sup>5</sup>) were administered via intravenous injection (n = 8-11 per group). Lungs were removed 14 days later, and tumor foci were counted. Additional mice (n = 8 per group) were killed, and peritoneal macrophages were assayed for cytotoxicity against the same mouse tumor cell line at various effector-to-target ratios. Both moderate exercise and ObetaG decreased lung tumor foci and increased macrophage cytotoxicity. However, there were no differences in lung tumor foci and macrophage cytotoxicity between Ex-ObetaG and either Ex-H<sub>2</sub>O or Con-ObetaG. These data suggest that, although not additive in their effects, both short-term moderate-exercise training and consumption of the soluble ObetaG can decrease the metastatic spread of injected B16 melanoma cells, and these effects may be mediated in part by an increase in macrophage cytotoxicity to B16 melanoma.

J Appl Physiol. 2004 Sep;97(3):955-9

### **RELATION BETWEEN CHANGES IN INTAKES OF DIETARY FIBER AND GRAIN PRODUCTS AND CHANGES IN WEIGHT AND DEVELOPMENT OF OBESITY AMONG MIDDLE-AGED WOMEN.**

BACKGROUND: Although increased consumption of dietary fiber and grain products is widely recommended to maintain healthy body weight, little is known about the relation of whole grains to body weight and long-term weight changes. OBJECTIVE: We examined the associations between the intakes of dietary fiber and whole- or refined-grain products and weight gain over time. DESIGN: In a prospective cohort study, 74,091 US female nurses, aged 38-63 y in 1984 and free of known cardiovascular disease, cancer, and diabetes at baseline, were followed from 1984 to 1996; their dietary habits were assessed in 1984, 1986, 1990, and 1994 with validated food-frequency questionnaires. Using multiple models to adjust for covariates, we calculated average weight, body mass index (BMI; in kg/m<sup>2</sup>), long-term weight changes, and the odds ratio of developing obesity (BMI > or = 30) according to change in dietary intake. RESULTS: Women who consumed more whole grains consistently weighed less than did women who consumed less whole grains (P for trend < 0.0001). Over 12 y, those with the greatest increase in intake of dietary fiber gained an average of 1.52 kg less than did those with the smallest increase in intake of dietary fiber (P for trend < 0.0001) independent of body weight at baseline, age, and changes in covariate status. Women in the highest quintile of dietary fiber intake had a 49% lower risk of major weight gain than did women in the highest quintile (OR = 0.51; 95% CI: 0.39, 0.67; P < 0.0001 for trend). CONCLUSION: Weight gain was inversely associated with the intake of high-fiber, whole-grain foods but positively related to the intake of refined-grain foods, which indicated the importance of distinguishing whole-grain products from refined-grain products to aid in weight control.

Am J Clin Nutr. 2003 Nov;78(5):920-7

### **LONG-TERM INTAKE OF DIETARY FIBER AND DECREASED RISK OF CORONARY HEART DISEASE AMONG WOMEN.**

CONTEXT: Epidemiological studies of men suggest that dietary fiber intake protects against coronary heart disease (CHD), but data on this association in women are sparse. OBJECTIVE: To examine the association between long-term intake of total dietary fiber as well as fiber from different sources and risk of CHD in women. DESIGN AND SETTING: The Nurses' Health Study, a large, prospective cohort study of US women followed up for 10 years from 1984. Dietary data were collected in 1984, 1986, and 1990, using a validated semiquantitative food frequency questionnaire. PARTICIPANTS: A total of 68,782 women aged 37 to 64

years without previously diagnosed angina, myocardial infarction (MI), stroke, cancer, hypercholesterolemia, or diabetes at baseline. MAIN OUTCOME MEASURE: Incidence of acute MI or death due to CHD by amount of fiber intake. RESULTS: Response rate averaged 80% to 90% during the 10-year follow-up. We documented 591 major CHD events (429 nonfatal MIs and 162 CHD deaths). The age-adjusted relative risk (RR) for major CHD events was 0.53 (95% confidence interval [CI], 0.40-0.69) for women in the highest quintile of total dietary fiber intake (median, 22.9 g/d) compared with women in the lowest quintile (median, 11.5 g/d). After controlling for age, cardiovascular risk factors, dietary factors, and multivitamin supplement use, the RR was 0.77 (95% CI, 0.57-1.04). For a 10-g/d increase in total fiber intake (the difference between the lowest and highest quintiles), the multivariate RR of total CHD events was 0.81 (95% CI, 0.66-0.99). Among different sources of dietary fiber (eg, cereal, vegetables, fruit), only cereal fiber was strongly associated with a reduced risk of CHD (multivariate RR, 0.63; 95% CI, 0.49-0.81 for each 5-g/d increase in cereal fiber). CONCLUSIONS: Our findings in women support the hypothesis that higher fiber intake, particularly from cereal sources, reduces the risk of CHD.

JAMA. 1999 Jun 2;281(21):1998-2004

## Diabetes

### ***Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis.***

CONTEXT: Inconsistent data suggest that endogenous sex hormones may have a role in sex-dependent etiologies of type 2 diabetes, such that hyperandrogenism may increase risk in women while decreasing risk in men. OBJECTIVE: To systematically assess studies evaluating the association of plasma levels of testosterone, sex hormone-binding globulin (SHBG), and estradiol with risk of type 2 diabetes. DATA SOURCES: Systematic search of EMBASE and MEDLINE (1966-June 2005) for English-language articles using the keywords diabetes, testosterone, sex-hormone-binding-globulin, and estradiol; references of retrieved articles; and direct author contact. STUDY SELECTION: From 80 retrieved articles, 43 prospective and cross-sectional studies were identified, comprising 6,974 women and 6,427 men and presenting relative risks (RRs) or hormone levels for cases and controls. DATA EXTRACTION: Information on study design, participant characteristics, hormone levels, and risk estimates were independently extracted by 2 investigators using a standardized protocol. DATA SYNTHESIS: Results were pooled using random effects and meta-regressions. Cross-sectional studies indicated that testosterone level was significantly lower in men with type 2 diabetes (mean difference, -76.6 ng/dL; 95% confidence interval [CI], -99.4 to -53.6) and higher in women with type 2 diabetes compared with controls (mean difference, 6.1 ng/dL; 95% CI, 2.3 to 10.1) ( $P < .001$  for sex difference). Similarly, prospective studies showed that men with higher testosterone levels (range, 449.6-605.2 ng/dL) had a 42% lower risk of type 2 diabetes (RR, 0.58; 95% CI, 0.39 to 0.87), while there was suggestion that testosterone increased risk in women ( $P = .06$  for sex difference). Cross-sectional and prospective studies both found that SHBG was more protective in women than in men ( $P < \text{or} = .01$  for sex difference for both), with prospective studies indicating that women with higher SHBG levels ( $>60$  vs  $< \text{or} = 60$  nmol/L) had an 80% lower risk of type 2 diabetes (RR, 0.20; 95% CI, 0.12 to 0.30), while men with higher SHBG levels ( $>28.3$  vs  $< \text{or} = 28.3$  nmol/L) had a 52% lower risk (RR, 0.48; 95% CI, 0.33 to 0.69). Estradiol levels were elevated among men and postmenopausal women with diabetes compared with controls ( $P = .007$ ). CONCLUSIONS: This systematic review indicates that endogenous sex hormones may differentially modulate glycemic status and risk of type 2 diabetes in men and women. High testosterone levels are associated with higher risk of type 2 diabetes in women but with lower risk in men; the inverse association of SHBG with risk was stronger in women than in men.

JAMA. 2006 Mar 15;295(11):1288-99

### **THE PITUITARY-GONADAL AXIS AND HEALTH IN ELDERLY MEN: A STUDY OF MEN BORN IN 1913.**

The results of recent studies suggest that a relative hypogonadism in men is associated with several established risk factors for prevalent diseases. Therefore, we determined total and free testosterone, luteinizing hormone (LH), and sex-hormone binding globulin (SHBG) in a cohort of randomly selected men ( $n = 659$ ) at 67 years of age. These data were analyzed cross-sectionally in relation to blood glucose and serum insulin, which were measured while fasting and after an oral glucose tolerance test, in addition to plasma lipids and blood pressure. The data were also analyzed in relation to impaired glucose tolerance (IGT) and diabetes, which were discovered at examination or earlier diagnosis. Risk factors for the development of diabetes up to 80 years of age were analyzed with univariate and multivariate statistics. Total and free testosterone and SHBG concentrations correlated negatively with glucose and insulin values; total testosterone and SHBG, with triglycerides; and SHBG, with blood pressure (from  $P < 0.05$  to  $P < 0.01$ ). Men with IGT or newly diagnosed diabetes had higher BMI values ( $26.2 \pm 0.31$  and  $27.0 \pm 0.59$  [mean  $\pm$  SE], respectively) and waist circumference ( $99.0 \pm 1.03$  and  $100.5 \pm 1.57$ ) than nondiabetic men (BMI,  $25.1 \pm 0.14$ ; waist circumference,  $95.4 \pm 0.47$ ;  $P < 0.05$ ), indicating abdominal obesity. Such men and men with previously diagnosed diabetes had, in general, lower total and free testosterone and SHBG levels, while those for LH were not different. In multivariate analyses that included BMI, waist-to-hip ratio, total and free testosterone, and SHBG, the remaining independent predictors for the development of diabetes were low total testosterone ( $P = 0.015$ ) and, on the borderline, low SHBG ( $P = 0.053$ ). In relation to nondiabetic men, the risk ratio for mortality, myocardial infarction, and stroke increased gradually and significantly from 1.18 to 1.68, from 1.51 to 1.78, and from 1.72 to 2.46 in men with IGT, newly diagnosed diabetes, and previously known diabetes, respectively. It was concluded that low testosterone and SHBG concentrations in elderly men are associated with established risk factors for diabetes and in established diabetes. Moreover, low testosterone levels independently predict the risk of developing diabetes. In different degrees of expression, the diabetic state predicts strongly (and gradually mortality from) myocardial infarction and stroke. It has been suggested that a relative hypogonadism might be a primary event, because other studies have shown that testosterone deficiency is followed by insulin resistance, which is ameliorated by testosterone substitution. The data suggest that the relative hypogonadism involved might be of both central and peripheral origin.

Diabetes. 1996 Nov;45(11):1605-9

## **ASSOCIATION OF OBESITY AND INSULIN RESISTANCE WITH SERUM TESTOSTERONE, SEX HORMONE BINDING GLOBULIN AND ESTRADIOL IN OLDER MALES.**

There is an increased accumulation of fat tissue with subsequent increase of insulin level, insulin resistance and decrease of testosterone level in aging males. AIM OF THE STUDY: Assessment of the relations between obesity, insulin resistance and levels of sex hormones. MATERIAL AND METHODS: Indices of obesity (BMI, WHR, waist circumference), insulin level, insulin resistance (HOMA-IR) and levels of sex hormones (total testosterone, free testosterone, free testosterone index, sex hormone-binding globulin--SHBG, estradiol) were measured in 107 males at the mean age of 60.1 +/- 7 years. RESULTS: Obesity among aging males is associated with insulin resistance and hyperinsulinism. All above factors correlate with decreased serum levels of testosterone and sex hormone binding globulin as well as increased ratio estradiol/testosterone ratio. CONCLUSION: Our data suggest a role of decreased levels of testosterone and SHBG in pathogenesis of visceral obesity and metabolic syndrome in older males.

Pol Merkur Lekarski. 2005 Nov;19(113):634-7

## **TESTOSTERONE REPLACEMENT THERAPY IMPROVES INSULIN RESISTANCE, GLYCAEMIC CONTROL, VISCERAL ADIPOSITY AND HYPERCHOLESTEROLAEMIA IN HYPOGONADAL MEN WITH TYPE 2 DIABETES.**

OBJECTIVE: Low levels of testosterone in men have been shown to be associated with type 2 diabetes, visceral adiposity, dyslipidaemia and metabolic syndrome. We investigated the effect of testosterone treatment on insulin resistance and glycaemic control in hypogonadal men with type 2 diabetes. DESIGN: This was a double-blind placebo-controlled crossover study in 24 hypogonadal men (10 treated with insulin) over the age of 30 years with type 2 diabetes. METHODS: Patients were treated with i.m. testosterone 200 mg every 2 weeks or placebo for 3 months in random order, followed by a washout period of 1 month before the alternate treatment phase. The primary outcomes were changes in fasting insulin sensitivity (as measured by homeostatic model index (HOMA) in those not on insulin), fasting blood glucose and glycated haemoglobin. The secondary outcomes were changes in body composition, fasting lipids and blood pressure. Statistical analysis was performed on the delta values, with the treatment effect of placebo compared against the treatment effect of testosterone. RESULTS: Testosterone therapy reduced the HOMA index (-1.73 +/- 0.67, P = 0.02, n = 14), indicating an improved fasting insulin sensitivity. Glycated haemoglobin was also reduced (-0.37 +/- 0.17%, P = 0.03), as was the fasting blood glucose (-1.58 +/- 0.68 mmol/l, P = 0.03). Testosterone treatment resulted in a reduction in visceral adiposity as assessed by waist circumference (-1.63 +/- 0.71 cm, P = 0.03) and waist/hip ratio (-0.03 +/- 0.01, P = 0.01). Total cholesterol decreased with testosterone therapy (-0.4 +/- 0.17 mmol/l, P = 0.03) but no effect on blood pressure was observed. CONCLUSIONS: Testosterone replacement therapy reduces insulin resistance and improves glycaemic control in hypogonadal men with type 2 diabetes. Improvements in glycaemic control, insulin resistance, cholesterol and visceral adiposity together represent an overall reduction in cardiovascular risk.

Eur J Endocrinol. 2006 Jun;154(6):899-906

## **PREVALENCE OF PROSTATE CANCER AMONG HYPOGONADAL MEN WITH PROSTATE-SPECIFIC ANTIGEN LEVELS OF 4.0 NG/ML OR LESS.**

OBJECTIVES: To determine the prevalence of prostate cancer in hypogonadal men with a prostate-specific antigen (PSA) level of 4.0 ng/mL or less. METHODS: A total of 345 consecutive hypogonadal men with a PSA level of 4.0 ng/mL or less underwent evaluation with digital rectal examination and prostate biopsy before initiating a program of testosterone replacement therapy. All men had low serum levels of total or free testosterone, defined as less than 300 and 1.5 ng/dL, respectively. RESULTS: Cancer was identified in 15.1%. The cancer detection rate was 5.6%, 17.5%, 26.4%, and 36.4% for a PSA level of 1.0 or less, 1.1 to 2.0, 2.1 to 3.0, and 3.1 to 4.0 ng/mL, respectively (P < 0.05). Cancer was detected in 26 (30.2%) of 86 men with a PSA level of 2.0 to 4.0 ng/mL. Cancer was detected in 21% of men with a testosterone level of 250 ng/dL or less compared with 12% of men with a testosterone level greater than 250 ng/dL (P = 0.04). Men with free testosterone levels of 1.0 ng/dL or less had a cancer rate of 20% compared with 12% for men with greater values (P = 0.04). The odds ratio of cancer detection for men in the lowest tertile compared with the highest tertile was 2.15 (95% confidence interval 1.01 to 4.55) for total testosterone and 2.26 (95% confidence interval 1.07 to 4.78) for free testosterone. CONCLUSIONS: Prostate cancer was present in more than 1 of 7 hypogonadal men with PSA of 4.0 ng/mL or less. An increased risk of prostate cancer was associated with more severe reductions in testosterone.

Urology. 2006 Dec;68(6):1263-7

## **DIFFERENT MECHANISMS IN TESTOSTERONE ACTION ON GLYCOGEN METABOLISM IN RAT PERINEAL AND SKELETAL MUSCLES.**

Testosterone affects glycogen levels in perineal and skeletal muscles by two distinct mechanisms. Both of them show similar sensitivity to androgens (0.1 mg/rat/day of testosterone being effective) and to antiandrogen administration. However, they differ because of the pattern of glycogen increase (early after the androgen injection in the perineal muscles; slowly and with a linear

function of time in the skeletal muscles), and because of the different sensitivities to adrenalectomy, diabetes and hypophysectomy. Also, the biochemical changes induced by testosterone in muscles differ. The rate of sugar uptake and phosphorylation is increased in the perineal muscle only; the rate of glucose incorporation into glycogen is increased in the perineal but depressed in the skeletal muscles. Therefore, in the former case glycogen accumulation depends mainly on increased synthesis; in the latter, it is probably the result of a glycogen sparing effect.

Endocrinology. 1975 Jan;96(1):77-84

**LIPOPHILIC AND HYDROPHILIC ANTIOXIDANT CAPACITIES OF COMMON FOODS IN THE UNITED STATES.**

Both lipophilic and hydrophilic antioxidant capacities were determined using the oxygen radical absorbance capacity (ORAC(FL)) assay with fluorescein as the fluorescent probe and 2,2'-azobis(2-amidinopropane) dihydrochloride as a peroxy radical generator on over 100 different kinds of foods, including fruits, vegetables, nuts, dried fruits, spices, cereals, infant, and other foods. Most of the foods were collected from four different regions and during two different seasons in U.S. markets. Total phenolics of each sample were also measured using the Folin-Ciocalteu reagent. Hydrophilic ORAC(FL) values (H-ORAC(FL)) ranged from 0.87 to 2641 micromol of Trolox equivalents (TE)/g among all of the foods, whereas lipophilic ORAC(FL) values (L-ORAC(FL)) ranged from 0.07 to 1611 micromol of TE/g. Generally, L-ORAC(FL) values were <10% of the H-ORAC(FL) values except for a very few samples. Total antioxidant capacity was calculated by combining L-ORAC(FL) and H-ORAC(FL). Differences of ORAC(FL) values in fruits and vegetables from different seasons and regions were relatively large for some foods but could not be analyzed in detail because of the sampling scheme. Two different processing methods, cooking and peeling, were used on selected foods to evaluate the impact of processing on ORAC(FL). The data demonstrated that processing can have significant effects on ORAC(FL). Considering all of the foods analyzed, the relationship between TP and H-ORAC(FL) showed a very weak correlation. Total hydrophilic and lipophilic antioxidant capacity intakes were calculated to be 5558 and 166 micromol of TE/day, respectively, on the basis of data from the USDA Continuing Survey of Food Intakes by Individuals (1994-1996).

J Agric Food Chem. 2004 Jun 16;52(12):4026-37

**INTERSPECIFIC VARIATION IN ANTHOCYANINS, PHENOLICS, AND ANTIOXIDANT CAPACITY AMONG GENOTYPES OF Highbush AND LOWbush BLUEBERRIES (Vaccinium SECTION CYANOCOCCUS spp.).**

Recent interest in the possible protective effects of dietary antioxidant compounds against human degenerative disease has prompted investigation of foods such as blueberries (*Vaccinium* sp.), which have a high antioxidant capacity. Fruit obtained from genotypes of highbush blueberries (*Vaccinium corymbosum* L.) and lowbush blueberries (*Vaccinium angustifolium* Aiton) were analyzed for their antioxidant capacity, their content of anthocyanins, and total phenolic compounds, to evaluate the intraspecific and interspecific variation in these parameters. The method of extraction influenced the composition of fruit extracts; the highest anthocyanin and total phenolic contents and antioxidant capacity were found in extracts obtained using a solvent of acidified aqueous methanol. Regardless of the method, lowbush blueberries were consistently higher in anthocyanins, total phenolics, and antioxidant capacity, compared with highbush blueberries. There was no relationship between fruit size and anthocyanin content in either species.

J Agric Food Chem. 2001 Oct;49(10):4761-7

**INHIBITORY EFFECTS OF BLUEBERRY EXTRACT ON THE PRODUCTION OF INFLAMMATORY MEDIATORS IN LIPOPOLYSACCHARIDE-ACTIVATED BV2 MICROGLIA.**

Sustained microglial activation in the central nervous system (CNS) has been extensively investigated in age-related neurodegenerative diseases and has been postulated to lead to neuronal cell loss in these conditions. Recent studies have shown that antiinflammatory drugs may suppress microglial activation and thus protect against microglial overactivation and subsequent cell loss. Research also suggests that fruits such as berries may contain both antioxidant and antiinflammatory polyphenols that may be important in this regard. Our previous research showed that blueberry extract was effective in preventing oxidant-induced calcium response deficits in M1 (muscarinic receptor)-transfected COS-7 cells. Extrapolating from these findings, the current study investigated the effect of blueberry extract on preventing inflammation-induced activation of microglia. Results indicated that treatments with blueberry extract inhibited the production of the inflammatory mediator nitric oxide (NO) as well as the cytokines interleukin-1 $\beta$  and tumor necrosis factor- $\alpha$ , in cell conditioned media from lipopolysaccharide (LPS)-activated BV2 microglia. Also, mRNA and protein levels of inducible nitric oxide synthase and cyclooxygenase-2 in LPS-activated BV2 cells were significantly reduced by treatments with blueberry extract. The results suggest that blueberry polyphenols attenuate inflammatory responses of brain microglia and could be potentially useful in modulation of inflammatory conditions in the CNS.

J Neurosci Res. 2007 Apr;85(5):1010-7

## THE BENEFICIAL EFFECTS OF FRUIT POLYPHENOLS ON BRAIN AGING.

Brain aging is characterized by the continual concession to battle against insults accumulated over the years. One of the major insults is oxidative stress, which is the inability to balance and to defend against the cellular generation of reactive oxygen species (ROS). These ROS cause oxidative damage to nucleic acid, carbohydrate, protein, and lipids. Oxidative damage is particularly detrimental to the brain, where the neuronal cells are largely post-mitotic. Therefore, damaged neurons cannot be replaced readily via mitosis. During normal aging, the brain undergoes morphological and functional modifications resulting in the observed behavioral declines such as decrements in motor and cognitive performance. These declines are augmented by neurodegenerative diseases including amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), and Parkinson's disease (PD). Research from our laboratory has shown that nutritional antioxidants, such as the polyphenols found in blueberries, can reverse age-related declines in neuronal signal transduction as well as cognitive and motor deficits. Furthermore, we have shown that short-term blueberry (BB) supplementation increases hippocampal plasticity. These findings are briefly reviewed in this paper.

Neurobiol Aging. 2005 Dec;26 Suppl 1:128-32

### **BLUEBERRY SUPPLEMENTATION ENHANCES SIGNALING AND PREVENTS BEHAVIORAL DEFICITS IN AN ALZHEIMER DISEASE MODEL.**

Previously, we showed that blueberry (BB) supplementation reversed the deleterious effects of aging on motor behavior and neuronal signaling in senescent rodents. We now report that BB-fed (from 4 months of age) APP + PS1 transgenic mice showed no deficits in Y-maze performance (at 12 months of age) with no alterations in amyloid beta burden. It appeared that the protective mechanisms are derived from BB-induced enhancement of memory-associated neuronal signaling (e.g. extracellular signal-regulated kinase) and alterations in neutral sphingomyelin-specific phospholipase C activity. Thus, our data indicate for the first time that it may be possible to overcome genetic predispositions to Alzheimer disease through diet.

Nutr Neurosci. 2003 Jun;6(3):153-62

### **BENEFICIAL EFFECTS OF FRUIT EXTRACTS ON NEURONAL FUNCTION AND BEHAVIOR IN A RODENT MODEL OF ACCELERATED AGING.**

Exposing young rats to particles of high-energy and charge (HZE particles) enhances indices of oxidative stress and inflammation and disrupts the functioning of the dopaminergic system and behaviors mediated by this system in a manner similar to that seen in aged animals. Previous research has shown that diets supplemented with 2% blueberry or strawberry extracts have the ability to retard and even reverse age-related deficits in behavior and signal transduction in rats, perhaps due to their antioxidant and anti-inflammatory properties. This study evaluated the efficacy of these diets on irradiation-induced deficits in these parameters by maintaining rats on these diets or a control diet for 8 weeks prior to being exposed to whole-body irradiation with 1.5Gy of 1GeV/n high-energy (56)Fe particles. Irradiation impaired performance in the Morris water maze and measures of dopamine release 1 month following radiation; these deficits were protected by the antioxidant diets. The strawberry diet offered better protection against spatial deficits in the maze because strawberry-fed animals were better able to retain place information (a hippocampally mediated behavior) compared to controls. The blueberry diet, on the other hand, seemed to improve reversal learning, a behavior more dependent on intact striatal function. These data suggest that (56)Fe particle irradiation causes deficits in behavior and signaling in rats which were ameliorated by an antioxidant diet and that the polyphenols in these fruits might be acting in different brain regions.

Neurobiol Aging. 2006 Jul 10; [Epub ahead of print]

### **FEEDING RATS DIETS ENRICHED IN LOWBUSH BLUEBERRIES FOR SIX WEEKS DECREASES ISCHEMIA-INDUCED BRAIN DAMAGE.**

Oxidative stress is an important element in the etiology of ischemic stroke. Lowbush blueberries (*Vaccinium angustifolium* Aiton) have a high antioxidant capacity and thus we determined whether consumption of lowbush blueberries would protect neurons from stroke-induced damage. Rats were fed AIN-93G diets containing 0 or 14.3% blueberries (g fresh weight/100 g feed) for 6 weeks. Stroke was then simulated by ligation of the left common carotid artery (ischemia), followed by hypoxia. One week later, plasma and urine were collected, and neuronal damage in the hippocampus was determined histologically. In control rats, hypoxia-ischemia resulted in 40 +/- 2% loss of neurons in the hippocampus of the left cerebral hemisphere, as compared to the right hemisphere. Rats on blueberry-supplemented diets lost only 17 +/- 2% of neurons in the ischemic hippocampus. Neuroprotection was observed in the CA1 and CA2 regions, but not CA3 region, of the hippocampus. The blueberry diet had no detectable effects on the plasma or urine oxygen radical absorbance capacity (ORAC) or plasma lipids. We conclude that consumption of lowbush blueberries by rats confers protection to the brain against damage from ischemia, suggesting that inclusion of blueberries in the diet may improve ischemic stroke outcomes.

## **BLACKBERRY, BLACK RASPBERRY, BLUEBERRY, CRANBERRY, RED RASPBERRY, AND STRAWBERRY EXTRACTS INHIBIT GROWTH AND STIMULATE APOPTOSIS OF HUMAN CANCER CELLS IN VITRO.**

Berry fruits are widely consumed in our diet and have attracted much attention due to their potential human health benefits. Berries contain a diverse range of phytochemicals with biological properties such as antioxidant, anticancer, anti-neurodegenerative, and anti-inflammatory activities. In the current study, extracts of six popularly consumed berries—blackberry, black raspberry, blueberry, cranberry, red raspberry and strawberry—were evaluated for their phenolic constituents using high performance liquid chromatography with ultraviolet (HPLC-UV) and electrospray ionization mass spectrometry (LC-ESI-MS) detection. The major classes of berry phenolics were anthocyanins, flavonols, flavanols, ellagitannins, gallotannins, proanthocyanidins, and phenolic acids. The berry extracts were evaluated for their ability to inhibit the growth of human oral (KB, CAL-27), breast (MCF-7), colon (HT-29, HCT116), and prostate (LNCaP) tumor cell lines at concentrations ranging from 25 to 200 micro g/mL. With increasing concentration of berry extract, increasing inhibition of cell proliferation in all of the cell lines were observed, with different degrees of potency between cell lines. The berry extracts were also evaluated for their ability to stimulate apoptosis of the COX-2 expressing colon cancer cell line, HT-29. Black raspberry and strawberry extracts showed the most significant pro-apoptotic effects against this cell line. The data provided by the current study and from other laboratories warrants further investigation into the chemopreventive and chemotherapeutic effects of berries using in vivo models.

J Agric Food Chem. 2006 Dec 13;54(25):9329-39

## **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

## **PTEROSTILBENE, AN ACTIVE CONSTITUENT OF BLUEBERRIES, SUPPRESSES ABERRANT CRYPT FOCI FORMATION IN THE AZOXYMETHANE-INDUCED COLON CARCINOGENESIS MODEL IN RATS.**

**PURPOSE:** Epidemiologic studies have linked the consumption of fruits and vegetables to reduced risk of several types of cancer. Laboratory animal model studies have provided evidence that stilbenes, phenolic compounds present in grapes and blueberries, play a role in inhibiting the risk of certain cancers. Pterostilbene, a naturally occurring stilbene from blueberries, was tested for its preventive activity against colon carcinogenesis. **EXPERIMENTAL DESIGN:** Experiments were designed to study the inhibitory effect of pterostilbene against the formation of azoxymethane-induced colonic aberrant crypt foci (ACF) preneoplastic lesions in male F344 rats. Beginning at 7 weeks of age, rats were treated with azoxymethane (15 mg/kg body weight s.c., once weekly for 2 weeks). One day after the second azoxymethane treatment, rats were fed experimental diets containing 0 or 40 ppm of pterostilbene. At 8 weeks after the second azoxymethane treatment, all rats were sacrificed, and colons were evaluated for ACF formation and for inhibition of inducible nitric oxide synthase (iNOS) and proliferating cell nuclear antigen. Effects on mucin MUC2 were also determined. **RESULTS:** Administration of pterostilbene for 8 weeks significantly suppressed azoxymethane-induced formation of ACF (57% inhibition,  $P < 0.001$ ) and multiple clusters of aberrant crypts (29% inhibition,  $P < 0.01$ ). Importantly, dietary pterostilbene also suppressed azoxymethane-induced colonic cell proliferation and iNOS expression. Inhibition of iNOS expression by pterostilbene was confirmed in cultured human colon cancer cells. **CONCLUSIONS:** The results of the present study suggest that pterostilbene, a compound present in blueberries, is of great interest for the prevention of colon cancer.

## **ANTI-DIABETIC PROPERTIES OF THE CANADIAN LOWBUSH BLUEBERRY VACCINIUM ANGUSTIFOLIUM AIT.**

Incidence of type II diabetes is rapidly increasing worldwide. In order to identify complementary or alternative approaches to existing medications, we studied anti-diabetic properties of *Vaccinium angustifolium* Ait., a natural health product recommended for diabetes treatment in Canada. Ethanol extracts of root, stem, leaf, and fruit were tested at 12.5 microg/ml for anti-diabetic activity in peripheral tissues and pancreatic beta cells using a variety of cell-based bioassays. Specifically, we assessed: (1) deoxyglucose uptake in differentiated C2C12 muscle cells and 3T3-L1 adipocytes; (2) glucose-stimulated insulin secretion (GSIS) in beta TC-tet pancreatic beta cells; (3) beta cell proliferation in beta TC-tet cells; (4) lipid accumulation in differentiating 3T3-L1 cells; (5) protection against glucose toxicity in PC12 cells. Root, stem, and leaf extracts significantly enhanced glucose transport in C2C12 cells by 15-25% in presence and absence of insulin after 20 h of incubation; no enhancement resulted from a 1 h exposure. In 3T3 cells, only the root and stem extracts enhanced uptake, and this effect was greater after 1 h than after 20 h; uptake was increased by up to 75% in absence of insulin. GSIS was potentiated by a small amount in growth-arrested beta TC-tet cells incubated overnight with leaf or stem extract. However, fruit extracts were found to increase 3H-thymidine incorporation in replicating beta TC-tet cells by 2.8-fold. Lipid accumulation in differentiating 3T3-L1 cells was accelerated by root, stem, and leaf extracts by as much as 6.5-fold by the end of a 6-day period. Stem, leaf, and fruit extracts reduced apoptosis by 20-33% in PC12 cells exposed to elevated glucose for 96 h. These results demonstrate that *V. angustifolium* contains active principles with insulin-like and glitazone-like properties, while conferring protection against glucose toxicity. Enhancement of proliferation in beta cells may represent another potential anti-diabetic property. Extracts of the Canadian blueberry thus show promise for use as a complementary anti-diabetic therapy.

Phytomedicine. 2006 Nov;13(9-10):612-23

## **EFFECTIVE SEPARATION OF POTENT ANTIPROLIFERATION AND ANTIADHESION COMPONENTS FROM WILD BLUEBERRY (VACCINIUM ANGUSTIFOLIUM AIT.) FRUITS.**

Extracts from wild blueberry (*Vaccinium angustifolium* Ait.) were separated into proanthocyanidin-rich fractions using liquid vacuum and open column chromatography on Toyopearl and Sephadex LH-20, respectively. Fractions were characterized using analytical tools including mass spectrometry and NMR spectroscopy; fraction composition was correlated with bioactivity using antiproliferation and antiadhesion in vitro assays. There was a significant positive correlation between proanthocyanidin content of different fractions and biological activity in both the antiproliferation and antiadhesion assays. Two fractions containing primarily 4→8-linked oligomeric proanthocyanidins with average degrees of polymerization (DPn) of 3.25 and 5.65 inhibited adhesion of *Escherichia coli* responsible for urinary tract infections. Only the fraction with a DPn of 5.65 had significant antiproliferation activity against human prostate and mouse liver cancer cell lines. These findings suggest both antiadhesion and antiproliferation activity are associated with high molecular weight proanthocyanidin oligomers found in wild blueberry fruits.

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