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**JOURNAL
ABSTRACTS****Prostate Cancer****ROLE OF MAMMALIAN LIGNANS IN THE PREVENTION AND TREATMENT OF PROSTATE CANCER.**

Prostate cancer is poised to become the most prevalent male cancer in the Western world. In Japan and China, incidence rates are almost 10-fold less those reported in the United States and the European Union. Epidemiological data suggest that environmental factors such as diet can significantly influence the incidence and mortality of prostate cancer. The differences in lifestyle between East and West are one of the major risk factors for developing prostate cancer. Traditional Japanese and Chinese diets are rich in foods containing phytoestrogenic compounds, whereas the Western diet is a poor source of these phytochemicals. The lignan phytoestrogens are the most widely occurring of these compounds. In vitro and in vivo reports in the literature indicate that lignans have the capacity to affect the pathogenesis of prostate cancer. However, their precise mechanism of action in prostate carcinogenesis remains unclear. This article outlines the possible role of lignans in prostate cancer by reviewing the current in vitro and in vivo evidence for their anticancer activities. The intriguing concept that lignans may play a role in the prevention and treatment of prostate cancer over the lifetime of an individual is discussed.

Nutr Cancer. 2005;52(1):1-14

DIETARY LIGNAN INTAKES AND RISK OF PRE- AND POSTMENOPAUSAL BREAST CANCER.

Lignans are plant compounds metabolized in the mammalian gut to produce the phytoestrogens enterolactone and enterodiol. Because estrogens have been linked to breast cancer etiology, lignans could affect breast cancer risk through modulation of endogenous estrogen metabolism or competitive inhibition with estrogen receptors. We examined breast cancer risk and dietary lignan intake in a population-based case-control study of 1,122 women with primary, incident, histologically confirmed breast cancer and 2,036 controls frequency matched to cases on age and county of residence as part of the Western New York Exposures and Breast Cancer (WEB) Study. Diet was assessed with a self-administered 104-item food frequency questionnaire and other relevant data were collected by detailed in-person interviews. Lignans were expressed as the sum of the dietary precursors secoisolariciresinol and matairesinol. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by unconditional logistic regression, adjusting for age, total energy and other breast cancer risk factors. Premenopausal women in the highest quartile of dietary lignan intake had reduced breast cancer risk (OR = 0.66; 95% CI = 0.44-0.98). No association was observed between lignan intakes and postmenopausal breast cancer. Our results suggest that dietary lignans may be important in the etiology of breast cancer, particularly among premenopausal women.

Int J Cancer. 2004 Sep 1;111(3):440-3

PHYTO-OESTROGENS AND RISK OF PROSTATE CANCER IN SCOTTISH MEN.

A population-based case-control study of diet, inherited susceptibility and prostate cancer was undertaken in the lowlands and central belt of Scotland to investigate the effect of phyto-oestrogen intake and serum concentrations on prostate cancer risk. A total of 433 cases and 483 controls aged 50-74 years were asked to complete a validated FFQ and provide a non-fasting blood sample. Multivariate logistic regression analysis found significant inverse associations with increased serum concentrations of enterolactone (adjusted OR 0.40, 95% CI 0.22, 0.71] and with the consumption of soy foods (adjusted OR 0.52, 95% CI 0.30, 0.91). However, no significant associations were observed for isoflavone intake or serum genistein, daidzein and equol. This study supports the hypotheses that soy foods and enterolactone metabolised from dietary lignans protect against prostate cancer in older Scottish men.

Br J Nutr. 2007 Aug;98(2):388-96

DIETARY PHYTOESTROGEN, SERUM ENTEROLACTONE AND RISK OF PROSTATE CANCER: THE CANCER PROSTATE SWEDEN STUDY (SWEDEN).

OBJECTIVE: Based on evidence that phytoestrogens may protect against prostate cancer, we evaluated the associations between serum enterolactone concentration or dietary phytoestrogen intake and risk of prostate cancer. **METHODS:** In our Swedish population-based case-control study, questionnaire-data were available for 1,499 prostate cancer cases and 1,130 controls, with serum enterolactone levels in a sub-group of 209 cases and 214 controls. Unconditional logistic regression was performed to estimate multivariate odds ratios (ORs) and 95% confidence intervals (CIs) for associations with risk of prostate cancer. **RESULTS:** High intake of food items rich in phytoestrogens was associated with a decreased risk of prostate cancer. The OR comparing the highest to the lowest quartile of intake was 0.74 (95% CI: 0.57-0.95; p-value for trend: 0.01). In contrast, we found no association between dietary intake of total or individual lignans or isoflavonoids and risk of prostate cancer. Intermediate serum levels of enterolactone were associated with a decreased risk of prostate cancer. The ORs comparing increasing quartiles of serum enterolactone concentration to the lowest quartile were, respectively, 0.28 (95% CI: 0.15-0.55), 0.63 (95% CI: 0.35-1.14) and 0.74 (95% CI: 0.41-1.32). **CONCLUSIONS:** Our results support the hypothesis that certain foods high in phytoestrogens are associated with a lower risk of prostate cancer.

Cancer Causes Control. 2006 Mar;17(2):169-80

EXPRESSION OF ENZYMES INVOLVED IN ESTROGEN METABOLISM IN HUMAN PROSTATE.

There is evidence that estrogens can directly modulate human prostate cell activity. It has also been shown that cultured human prostate cancer LNCaP can synthesize the active estrogen estradiol (E2). To elucidate the metabolism of estrogens in the human prostate, we have studied the expression of enzymes involved in the formation and inactivation of estrogens at the cellular level. 17beta-Hydroxy-steroid dehydrogenase (17beta-HSD) types 1, 2, 4, 7, and 12, as well as aromatase mRNA and protein expressions, were studied in benign prostatic hyperplasia (BPH) specimens using in situ hybridization and immunohistochemistry. For 17beta-HSD type 4, only in situ hybridization studies were performed. Identical results were obtained with in situ hybridization and immunohistochemistry. All the enzymes studied were shown to be expressed in both epithelial and stromal cells, with the exception of 17beta-HSD types 4 and 7, which were detected only in the epithelial cells. On the basis of our previous results, showing that 3beta-HSD and 17beta-HSD type 5 are expressed in human prostate, and of the present data, it can be concluded that the human prostate expresses all the enzymes involved in the conversion of circulating dehydroepiandrosterone (DHEA) to E2. The local biosynthesis of E2 might be involved in the development and/or progression of prostate pathology such as BPH and prostate cancer through modulation of estrogen receptors, which are also expressed in epithelial and stromal cells.

J Histochem Cytochem. 2006 Aug;54(8):911-21

MAMMALIAN LIGNANS AND GENISTEIN DECREASE THE ACTIVITIES OF AROMATASE AND 17BETA-HYDROXYSTEROID DEHYDROGENASE IN MCF-7 CELLS.

Estrogen plays a major role in breast cancer development and progression. Breast tissue and cell lines contain the necessary enzymes for estrogen synthesis, including aromatase and 17beta-hydroxysteroid dehydrogenase (17beta-HSD). These enzymes can influence tissue exposure to estrogen and therefore have become targets for breast cancer treatment and prevention. This study determined whether the isoflavone genistein (GEN) and the mammalian lignans enterolactone (EL) and enterodiol (ED) would inhibit the activity of aromatase and 17beta-HSD type 1 in MCF-7 cancer cells, thereby decreasing the amount of estradiol (E2) produced and consequently cell proliferation. Results showed that 10 microM EL, ED and GEN significantly decreased the amount of estrone (E1) produced via the aromatase pathway by 37%, 81%, and 70%, respectively. Regarding 17beta-HSD type 1, 50 microM EL and GEN maximally inhibited E2 production by 84% and 59%, respectively. The reduction in E1 and E2 production by EL and the reduction in E2 production by GEN were significantly related to a reduction in MCF-7 cell proliferation. 4-Hydroxyandrostene-3,17-dione (50 microM) did not inhibit aromatase but inhibited the conversion of E1 to E2 by 78%, suggesting that it is a 17beta-HSD type 1 inhibitor. In conclusion, modulation of local E2 synthesis is one potential mechanism through which ED, EL and GEN may protect against breast cancer.

J Steroid Biochem Mol Biol. 2005 Apr;94(5):461-7

LOW TESTOSTERONE LEVELS ARE ASSOCIATED WITH CORONARY ARTERY DISEASE IN MALE PATIENTS WITH ANGINA.

Historically, high androgen levels have been linked with an increased risk for coronary artery disease (CAD). However, more recent data suggest that low androgen levels are associated with adverse cardiovascular risk factors, including an atherogenic lipid profile, obesity and insulin resistance. The aim of the present study was to evaluate the relationship between plasma sex hormone levels and presence and degree of CAD in patients undergoing coronary angiography and in matched controls. We evaluated 129 consecutive male patients (mean age 58+/-4 years, range 43-72 years) referred for diagnostic coronary angiography because of symptoms suggestive of CAD, but without acute coronary syndromes or prior diagnosis of hypogonadism. Patients were matched with healthy volunteers. Out of 129 patients, 119 had proven CAD; in particular, 32 of them had one, 63 had two and 24 had three vessel disease, respectively. Patients had significantly lower levels of testosterone

than controls (9.8+/-6.5 and 13.5+/-5.4 nmol/l, P<0.01) and higher levels of gonadotrophin (12.0+/-1.5 vs 6.6+/-1.9 IU/l and 7.9+/-2.1 vs 4.4+/-1.4, P<0.01 for follicle-stimulating hormone and luteinizing hormone, respectively). Also, both bioavailable testosterone and plasma oestradiol levels were lower in patients as compared to controls (0.84+/-0.45 vs 1.19+/-0.74 nmol/l, P<0.01 and 10.7+/-1.4 vs 13.3+/-3.5 pg/ml, P<0.05). Hormone levels were compared in cases with one, two or three vessel disease showing significant differences associated with increasing severity of coronary disease. An inverse relationship between the degree of CAD and plasma testosterone levels was found (r=-0.52, P<0.01). In conclusion, patients with CAD have lower testosterone and oestradiol levels than healthy controls. These changes are inversely correlated to the degree of CAD, suggesting that low plasma testosterone may be involved with the increased risk of CAD in men.

Int J Impot Res. 2007 Mar-Apr;19(2):176-82

TESTOSTERONE USE IN MEN WITH SEXUAL DYSFUNCTION:A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED PLACEBO-CONTROLLED TRIALS.

OBJECTIVE: To conduct a systematic review and meta-analysis of randomized placebo-controlled trials to measure the effect of testosterone use on sexual function in men with sexual dysfunction and varying testosterone levels. **METHODS:** Librarian-designed search strategies were used to search the MEDLINE (1966 to October 2004), EMBASE (1988 to October 2004), and Cochrane CENTRAL (inception to October 2004) databases. The MEDLINE search was rerun in March 2005. We also reviewed reference lists from included studies and content expert files. We selected randomized placebo-controlled trials of testosterone vs placebo that enrolled men with sexual dysfunction and measured satisfaction with erectile function and libido and overall sexual satisfaction. **RESULTS:** We included 17 trials (N = 862 participants) in this review. Trials that enrolled participants with low testosterone levels showed (1) a moderate insignificant and inconsistent effect of testosterone use on satisfaction with erectile function (random-effects pooled effect size, 0.80; 95% confidence interval [CI], -0.10 to 1.60), (2) a large effect on libido (pooled effect size, 1.31; 95% CI, 0.40 to 2.25), and (3) no significant effect on overall sexual satisfaction. Trials that enrolled patients with low-normal and normal testosterone levels at baseline showed testosterone that caused (1) a small effect on satisfaction with erectile function (pooled effect size, 0.34; 95% CI, 0.03 to 0.65), (2) moderate nonsignificant effect on libido (pooled effect size, 0.41; 95% CI, -0.01 to 0.83), and (3) no significant effect on overall sexual satisfaction. **CONCLUSION:** Testosterone use in men is associated with small improvements in satisfaction with erectile function and moderate improvements in libido. Unexplained inconsistent results across trials, wide CIs, and possible reporting bias weaken these inferences.

Mayo Clin Proc. 2007 Jan;82(1):20-8

FLAXSEED AND ITS LIGNANS INHIBIT ESTRADIOL-INDUCED GROWTH, ANGIOGENESIS, AND SECRETION OF VASCULAR ENDOTHELIAL GROWTH FACTOR IN HUMAN BREAST CANCER XENOGRAPTS IN VIVO.

PURPOSE: Vascular endothelial growth factor (VEGF) is a potent stimulator of angiogenesis, which is crucial in cancer progression. We have previously shown that estradiol (E2) increases VEGF in breast cancer. Phytoestrogens are potential compounds in breast cancer prevention and treatment by poorly understood mechanisms. The main phytoestrogens in Western diet are lignans, and flaxseed is a rich source of the mammalian lignans enterodiol and enterolactone. **EXPERIMENTAL DESIGN:** In the present study, ovariectomized mice were treated with continuous release of E2. MCF-7 tumors were established and mice were fed with basal diet or 10% flaxseed, and two groups that were fed basal diet received daily injections with enterodiol or enterolactone (15 mg/kg body weight). **RESULTS:** We show that flaxseed, enterodiol, and enterolactone counteracted E2-induced growth and angiogenesis in solid tumors. Extracellular VEGF in vivo, sampled using microdialysis, in all intervention groups was significantly decreased compared with tumors in the basal diet group. Our in vivo findings were confirmed in vitro. By adding enterodiol or enterolactone, E2-induced VEGF secretion in MCF-7 cells decreased significantly without agonistic effects. The increased VEGF secretion by E2 in MCF-7 cells increased the expression of VEGF receptor-2 in umbilical vein endothelial cells, suggesting a proangiogenic effect by E2 by two different mechanisms, both of which were inhibited by the addition of lignans. **CONCLUSIONS:** Our results suggest that flaxseed and its lignans have potent antiestrogenic effects on estrogen receptor-positive breast cancer and may prove to be beneficial in breast cancer prevention strategies in the future.

Clin Cancer Res. 2007 Feb 1;13(3):1061-7

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CORRELATION BETWEEN HELICOBACTER PYLORI INFECTION, GASTRIC DISEASES AND LIFE HABITS AMONG PATIENTS TREATED AT A UNIVERSITY HOSPITAL IN SOUTHEAST BRAZIL.

Helicobacter pylori is considered a significant agent in the development of various gastric diseases. However, the diseases caused by this bacterium are known as being multi-factorial, with the genotype, immune system and life habits of the host playing important roles in the establishment of the clinical outcome. Also, *H. pylori* exhibit a high degree of genetic variability, contributing to the complexity of the host-pathogen relationship. These observations, considered together with the widely-varying origins and social habits of the Brazilian population, lead us to speculate about the influence of these life habits on *H. pylori* infection and the clinical outcome. Therefore, in this study we evaluated the relationship between *H. pylori* infection and certain diseases in 172 patients treated at the Hospital das Clínicas of Ribeirão Preto (HCRP), Brazil, taking into account their different life habits, such as non-steroidal anti-inflammatory drugs and alcohol ingestion, and smoking habit. Our analysis indicated that *H. pylori* infection is not affected by any of the life habits evaluated but is associated with the development of peptic ulcers (gastric and duodenal ulcer) and inverse correlate with gastroesophageal reflux disease (GERD). No correlation was found between the infection with this bacterium and gastritis or intestinal metaplasia. However, gastritis and erosive gastritis were directly correlated with non-steroidal anti-inflammatory drugs (NSAID) ingestion. Moreover, ingestion of alcohol beverages exhibited a protective effect on gastritis development in men. Our data also indicated that to achieve reliable detection of this bacterium in biopsies, two or three detection methods should be used.

Braz J Infect Dis. 2007 Feb;11(1):89-95

H PYLORI INFECTION AND OTHER RISK FACTORS ASSOCIATED WITH PEPTIC ULCERS IN TURKISH PATIENTS: A RETROSPECTIVE STUDY.

AIM: To identify and evaluate the relative impact of *H pylori* infection and other risk factors on the occurrence of gastric ulcer (GU), duodenal ulcer (DU) and gastritis in Turkish patients. **METHODS:** A total of 4,471 patients (48.3% female) out of 4863 attended the Samatya hospital in Istanbul (June 1999-October 2003) were included. The records of *H pylori* status (CLO-test), endoscopic findings of GU, DU and gastritis, personal habits (smoking, alcohol intake) and medication [non-steroidal anti-inflammatory drugs (NSAIDs), aspirin intake] were analyzed using multi-way frequency analysis. **RESULTS:** We have found that GU in the presence of *H pylori* had significant association with aspirin ($P=0.0001$), alcohol ($P=0.0090$) and NSAIDs ($P=0.0372$). DU on the other hand had significant association with aspirin/smoking/NSAIDs ($P=0.0259$), aspirin/alcohol ($P=0.0002$) and aspirin/smoking ($P=0.0233$), also in the presence of *H pylori*. In the absence of *H pylori* GU had significant association with alcohol/NSAIDs ($P=0.0431$), and NSAIDs ($P=0.0436$). While DU in the absence of *H pylori* had significant association with smoking/alcohol/ NSAIDs ($P=0.0013$), aspirin/NSAIDs ($P=0.0334$), aspirin/alcohol ($P=0.0360$). **CONCLUSION:** In the presence of *H pylori*, aspirin, alcohol and NSAIDs intake act as an independent risk factors that had an augmenting impact on the occurrence of GU and only together on the occurrence of DU in Turkish patients.

World J Gastroenterol. 2007 Jun 21;13(23):3245-8

NEW MOLECULAR MECHANISMS OF DUODENAL ULCERATION.

Stress is a major etiologic factor in the pathogenesis of gastric & duodenal ulceration, as first described in rats by Hans Selye. In patients with "peptic ulcers" duodenal ulcers (DU) are more frequent than gastric ulcers (except in Japan). Thus, our research during the last 3 decades focused on the molecular mechanisms of DU in rodent models of chemically induced DU, and here we review our 3 recent findings: Endothelins (ET-1), the immediate early gene *egr-1* & imbalance of angiogenic/anti-angiogenic molecules. Namely, we found an enhanced expression & release of ET-1 within 15-30 min after the administration of duodenal ulcerogen cysteamine, resulting in local ischemia that triggers the expression of hypoxia-inducible factors (HIF-1α). Our gene expression studies also revealed an early (0.5-2 hr) increase in the expression of *egr-1* that is followed (12-24 hr) by upregulation of angiogenic growth factors (e.g., VEGF, bFGF, PDGF). Surprisingly, this event is also associated with an enhanced production of angiostatin & endostatin that probably counteract the beneficial effect of angiogenic molecules. Thus, the initial injury to endothelial & epithelial cells in DU seems to be aggravated (& not initiated) by HCl & proteolytic enzymes. The resulting mucosal necrosis does not rapidly heal because of the imbalance of VEGF & angiostatin/endostatin, hence duodenal ulcers develop. The experimental ulcers Selye described morphologically are now characterized at the molecular & genome level, involving unexpected mediators like ET-1, *egr-1* & angiogenesis-related molecules.

INFLAMMATION, ATROPHY, AND GASTRIC CANCER.

The association between chronic inflammation and cancer is now well established. This association has recently received renewed interest with the recognition that microbial pathogens can be responsible for the chronic inflammation observed in many cancers, particularly those originating in the gastrointestinal system. A prime example is *Helicobacter pylori*, which infects 50% of the world's population and is now known to be responsible for inducing chronic gastric inflammation that progresses to atrophy, metaplasia, dysplasia, and gastric cancer. This Review provides an overview of recent progress in elucidating the bacterial properties responsible for colonization of the stomach, persistence in the stomach, and triggering of inflammation, as well as the host factors that have a role in determining whether gastritis progresses to gastric cancer. We also discuss how the increased understanding of the relationship between inflammation and gastric cancer still leaves many questions unanswered regarding recommendations for prevention and treatment.

J Clin Invest. 2007 Jan;117(1):60-9

HELICOBACTER PYLORI AND BENIGN UPPER DIGESTIVE DISEASE.

Acute infection with *Helicobacter pylori* causes hypo-chlorhydria and gastrointestinal upset. As the infection persists, patients develop chronic antral-predominant or pangastritis. Gastric and duodenal ulcers arise from chronic mucosal inflammation and disordered acid secretion in the stomach. With successful eradication of *H. pylori*, non-NSAID-related gastric and duodenal ulcers heal even without long-term acid suppression. More importantly, peptic ulcers and their complications rarely recur. Clearing *H. pylori* infection also reduces the risk of mucosal injury in NSAID and aspirin users; the protective effects are more pronounced in NSAID-naïve and aspirin users. *H. pylori* is unlikely to be the cause of gastro-oesophageal reflux disease. However, a patient's reflux symptoms may be more difficult to control after clearing the infection. Although there is little evidence to support a causal relationship between *H. pylori* and non-ulcer dyspepsia, treatment of the infection gives a modest improvement of symptoms.

Best Pract Res Clin Gastroenterol. 2007;21(2):261-79

THE INFLAMMATORY AND IMMUNE RESPONSE TO HELICOBACTER PYLORI INFECTION.

Lifelong *Helicobacter pylori* infection and its associated gastric inflammation underlie peptic ulceration and gastric carcinogenesis. The immune and inflammatory responses to *H. pylori* are doubly responsible: gastric inflammation is the main mediator of pathology, and the immune and inflammatory response is ineffective, allowing lifelong bacterial persistence. However, despite inducing gastric inflammation, most infections do not cause disease, and bacterial, host and environmental factors determine individual disease risk. Although *H. pylori* avoids many innate immune receptors, specific virulence factors (including those encoded on the *cag* pathogenicity island) stimulate innate immunity to increase gastric inflammation and increase disease risk. An acquired T helper 1 response upregulates local immune effectors. The extent to which environmental factors (including parasite infection), host factors and *H. pylori* itself influence T-helper differentiation and regulatory T-cell responses remains controversial. Finally, effective vaccines have still not been developed: a better understanding of the immune response to *H. pylori* may help.

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Gastric cancer remains a major health burden on many societies claiming hundreds of thousands of lives every year. The discovery of *Helicobacter pylori* has no doubt revolutionised our understanding of this malignancy, which is now regarded as a paradigm for infection-induced chronic inflammation-mediated cancer. In this paper, we discuss the evidence for the association between *H. pylori* and gastric adenocarcinoma and MALT lymphoma. We also discuss the pathogenesis of these two forms of cancer and the factors that determine their outcome. There is no doubt that the knowledge accumulated over the past two decades will be translated into eventual victory over this killer cancer, largely because we now appreciate that the best way to prevent the cancer is by preventing acquisition of the infection in the first place, or by eradicating the infection in infected subjects. Defining the optimal timing of intervention is going to be the challenge facing us over the next two decades.

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Best Pract Res Clin Gastroenterol. 2007;21(2):281-97

CYTOKINE IMBALANCE IN THE PATHOPHYSIOLOGY OF MAJOR DEPRESSIVE DISORDER.

OBJECTIVE: A substantial body of evidence indicates that dysregulation of the immune system is associated with Major Depressive Disorder (MDD). Because most cytokines have pleiotropic effects, we measured various subsets of cytokines to examine the association between immune response and MDD. **METHODS:** Forty-eight hospitalized MDD patients and 63 normal controls were recruited. We measured in vitro monocytic (IL-6 and tumor necrosis factor (TNF)-alpha), Th1 (interferon (IFN)-gamma and interleukin (IL)-2), Th2 (IL-4), and Treg (transforming growth factor (TGF)-beta1) cytokine production as well as IL-2/IL-4 and IFN-gamma/IL-4 ratios for both groups. Depressive symptoms were assessed by Hamilton Depression Rating Scale. Patients were evaluated before and after 6 weeks of antidepressant treatment. **RESULTS:** At admission, IL-6, TNF-alpha, TGF-beta1 production, and IFN-gamma/IL-4 ratio were significantly higher, whereas IFN-gamma, IL-2, and IL-4 were significantly lower in MDD patients. After treatment, IL-6 and TGF-beta1 production were significantly lower than before treatment. **CONCLUSION:** We suggest that activation of monocytic proinflammatory cytokines, and inhibition of both Th1 and Th2 cytokines may be associated with immunological dysregulation in MDD. TGF-beta1 may be associated with the regulation of monocytic cytokines as well as Th1 and Th2 cytokines in MDD.

Prog Neuropsychopharmacol Biol Psychiatry. 2007 Jun 30;31(5):1044-53

CYTOKINES AND LATE-LIFE DEPRESSION.

Cytokines are peripherally and centrally produced proteins that regulate immune and immunological responses. They also have neurochemical, neuroendocrine and behavioral effects similar to those seen in patients with depression. A review of the literature reveals several cytokines, including IL-1beta, IL-2, IL-6 and IFN, have been shown to be elevated in plasma of working-age adults with depression and dysthymia. A more detailed review of the literature also reveals similar associations between cytokines and late-life depression, with IL-1beta, IL-6 and TNF-alpha all being reported to be elevated in both depression and dysthymia. It has been hypothesized that cytokines provide the link between depression, neurochemical changes and the altered HPA axis that are known to occur in this disease, and evidence is presented that supports this view. However, the evidence that antidepressants may have effects on cytokines is conflicting. Increased cytokine levels may also serve as an explanation for the increased risk for vascular disease that has been associated with depression, and a possible mechanism for this is discussed.

Essent Psychopharmacol. 2006;7(1):42-52

PLASMA CYTOKINE PROFILES IN DEPRESSED PATIENTS WHO FAIL TO RESPOND TO SELECTIVE SEROTONIN REUPTAKE INHIBITOR THERAPY.

OBJECTIVE: Approximately 30% of patients with depression fail to respond to a selective serotonin reuptake inhibitor (SSRI). Few studies have attempted to define these patients from a biological perspective. Studies suggest that overall patients with depression show increased production of proinflammatory cytokines. We examined pro- and anti-inflammatory cytokine levels in patients who were SSRI resistant. **METHODS:** Plasma concentrations of IL-6, IL-8, IL-10, TNF-alpha and sIL-6R were measured with enzyme linked immunosorbent assays (ELISA) in DSM-1V major depressives who were SSRI resistant, in formerly SSRI resistant patients currently euthymic and in healthy controls. **RESULTS:** Patients with SSRI-resistant depression had significantly higher production of the pro-inflammatory cytokines IL-6 ($p=0.01$) and TNF-alpha ($p=0.004$) compared to normal controls. Euthymic patients who were formerly SSRI resistant had proinflammatory cytokine levels which were similar to the healthy subject group. Anti-inflammatory cytokine levels did not differ across the 3 groups. **CONCLUSION:** Suppression of proinflammatory cytokines does not occur in depressed patients who fail to respond to SSRIs and is necessary for clinical recovery.

J Psychiatr Res. 2007 Apr-Jun;41(3-4):326-31

ANTIDEPRESSANT THERAPY AND C-REACTIVE PROTEIN LEVELS.

BACKGROUND: Major depression is associated with activation of the inflammatory response. **AIMS:** To examine C-reactive protein levels in depression and to determine the impact of selective serotonin reuptake inhibitor (SSRI) therapy. **METHOD:** A two-part study. In study 1, which used a between-subjects design, C-reactive protein was measured in 32 patients (20 currently

depressed, 12 euthymic) with a history of DSM-IV major depression, all of whom were treated with an SSRI, and in a healthy comparison group (n = 20). Study 2 employed a within-subject design: C-reactive protein was measured in 20 patients with major depression both before and after SSRI treatment. RESULTS: In study 1, C-reactive protein levels did not differ between the group with depressive disorder (either currently depressed or euthymic) treated with SSRIs and the healthy group. In study 2 the protein levels dropped significantly following treatment with antidepressant medication. CONCLUSIONS: Following SSRI treatment for major depression there is a significant drop in C-reactive protein concentrations whether or not the depression resolves. These findings indicate that antidepressants induce an anti-inflammatory response independent of antidepressant action.

Br J Psychiatry. 2006 May;188:449-52

PLASMA LEVELS OF ADIPONECTIN AND TUMOR NECROSIS FACTOR-ALPHA IN PATIENTS WITH REMITTED MAJOR DEPRESSION RECEIVING LONG-TERM MAINTENANCE ANTIDEPRESSANT THERAPY.

Adiponectin, an adipose tissue-specific plasma protein, is involved in insulin sensitization and has anti-atherosclerotic properties, whereas tumor necrosis factor-alpha (TNF-alpha), a pro-inflammatory protein, plays important roles in inflammatory endothelial injury and atherosclerotic changes. It has been reported that adiponectin and TNF-alpha inhibit each other's expression and production in adipocytes. Several in vitro studies indicated that antidepressant medications decreased the production of pro-inflammatory cytokines including TNF-alpha, but the effect of antidepressants on the expression of adiponectin is still unknown. We examined the plasma levels of TNF-alpha and adiponectin in patients with remitted depression receiving maintenance antidepressant therapy for longer than half a year, and compared the levels with those in healthy controls. The plasma levels of TNF-alpha and adiponectin in the remitted depression group were significantly lower and higher than those in the control group, respectively. This preliminary cross-sectional study suggests the possibility that maintenance antidepressant therapy may have anti-inflammatory effects and prevent the development of atherosclerosis.

Prog Neuropsychopharmacol Biol Psychiatry. 2006 Aug 30;30(6):1159-62

EVIDENCE FOR LOW-GRADE SYSTEMIC PROINFLAMMATORY ACTIVITY IN PATIENTS WITH POSTTRAUMATIC STRESS DISORDER.

Posttraumatic stress disorder (PTSD) may increase cardiovascular risk but the psychophysiological mechanisms involved are elusive. We hypothesized that proinflammatory activity is elevated in patients with PTSD as diagnosed by the Clinician Administered PTSD Scale (CAPS) interview. Plasma levels of proinflammatory C-reactive protein (CRP), interleukin (IL)-1beta, IL-6, and tumor necrosis factor (TNF)-alpha, and of anti-inflammatory IL-4 and IL-10 were measured in 14 otherwise healthy PTSD patients and in 14 age- and gender-matched healthy non-PTSD controls. Levels of TNF-alpha (p=0.038; effect size Cohen's d=0.58) and of IL-1beta (p=0.075, d=0.68) were higher in patients than in controls. CRP (d=0.10), IL-6 (d=0.18), IL-4 (d=0.42), and IL-10 (d=0.37) were not significantly different between groups. Controlling for traditional cardiovascular risk factors, mood, and time since trauma revealed lower IL-4 in patients than in controls (p=0.029) and rendered group differences in TNF-alpha and IL-1beta insignificant. In all subjects, TNF-alpha correlated with total (frequency and intensity) PTSD symptom cluster of re-experiencing (r=0.49, p=0.008), avoidance (r=0.37, p=0.050), and hyperarousal (r=0.42, p=0.026), and with PTSD total symptom score (r=0.37, p=0.054). Controlling for time since trauma attenuated these associations. The correlation between IL-1beta and total avoidance symptoms (r=0.42, p=0.028) became insignificant when controlling for anxiety and depression. IL-4 correlated with total hyperarousal symptoms (r=-0.38, p=0.047), and after controlling for systolic blood pressure and smoking status, with PTSD total symptom score (r=-0.41, p=0.035). PTSD patients showed a low-grade systemic proinflammatory state, which, moreover, was related to PTSD symptom levels suggesting one mechanism by which PTSD could contribute to atherosclerotic disease.

J Psychiatr Res. 2007 Nov;41(9):744-52

SPECIFIC BRAIN REGIONS OF FEMALE RATS ARE DIFFERENTIALLY DEPLETED OF DOCOSAHEXAENOIC ACID BY REPRODUCTIVE ACTIVITY AND AN (N-3) FATTY ACID-DEFICIENT DIET.

Low tissue levels of (n-3) PUFA, particularly docosahexaenoic acid [DHA, 22:6(n-3)], are implicated in postpartum depression. Brain DHA content is depleted in female rats undergoing pregnancy and lactation when the diet supplies inadequate (n-3) PUFA. In this study, the effects of DHA depletion as a result of reproductive activity and an (n-3) PUFA-deficient diet were examined in 8 specific brain regions of female rats after undergoing 2 sequential reproductive cycles. Virgin females, fed the alpha-linolenic acid (ALA)-containing or deficient (low-ALA) diets for a commensurate duration (13 wk) served as a control for reproduction. Total phospholipid composition of each brain region was determined at weaning (postnatal d 21) by TLC/GC. The regional PUFA composition of ALA virgins was similar to that previously measured in male rats. All brain regions examined were affected by reproductive activity and/or the low-ALA diet; however, the magnitude of the loss of DHA and compensatory incorporation of docosapentaenoic acid [(n-6) DPA, 22:5(n-6)] varied among brain regions. In low-ALA parous dams, frontal cortex (77% of ALA virgin) and temporal lobe (83% of ALA virgin), regions involved in cognition and affect, were among those exhibiting the greatest depletion of DHA. Caudate-putamen also exhibited significant depletion of DHA (82% of ALA virgin), whereas only (n-6) DPA

levels were altered in ventral striatum, hypothalamus, hippocampus, and cerebellum. This pattern of changes in regional DHA and (n-6) DPA content suggests that specific neuronal systems may be differentially affected by depletion of brain DHA in the postpartum organism.

J Nutr. 2007 Jan;137(1):130-4

OMEGA-3 POLYUNSATURATED ESSENTIAL FATTY ACID STATUS AS A PREDICTOR OF FUTURE SUICIDE RISK.

OBJECTIVE: Low levels of docosahexaenoic acid, a polyunsaturated fatty acid, and elevated ratios of omega-6/omega-3 fatty acids are associated with major depression and, possibly, suicidal behavior. Predicting risk of future suicidal behaviors by essential fatty acid status merits examination. **METHOD:** Plasma polyunsaturated fatty acid levels in phospholipids were measured in 33 medication-free depressed subjects monitored for suicide attempt over a 2-year period. Survival analysis examined the association of plasma polyunsaturated fatty acid status and pathological outcome. **RESULTS:** Seven subjects attempted suicide on follow-up. A lower docosahexaenoic acid percentage of total plasma polyunsaturated fatty acids and a higher omega-6/omega-3 ratio predicted suicide attempt. **CONCLUSIONS:** A low docosahexaenoic acid percentage and low omega-3 proportions of lipid profile predicted risk of suicidal behavior among depressed patients over the 2-year period. If confirmed, this finding would have implications for the neurobiology of suicide and reduction of suicide risk.

Am J Psychiatry. 2006 Jun;163(6):1100-2

ASSESSING PROSTATE CANCER RISK: RESULTS FROM THE PROSTATE CANCER PREVENTION TRIAL.

BACKGROUND: Prostate-specific antigen (PSA) testing is the primary method used to diagnose prostate cancer in the United States. Methods to integrate other risk factors associated with prostate cancer into individualized risk prediction are needed. We used prostate biopsy data from men who participated in the Prostate Cancer Prevention Trial (PCPT) to develop a predictive model of prostate cancer. **METHODS:** We included 5,519 men from the placebo group of the PCPT who underwent prostate biopsy, had at least one PSA measurement and a digital rectal examination (DRE) performed during the year before the biopsy, and had at least two PSA measurements performed during the 3 years before the prostate biopsy. Logistic regression was used to model the risk of prostate cancer and high-grade disease associated with age at biopsy, race, family history of prostate cancer, PSA level, PSA velocity, DRE result, and previous prostate biopsy. Risk equations were created from the estimated logistic regression models. All statistical tests were two-sided. **RESULTS:** A total of 1211 (21.9%) men were diagnosed with prostate cancer by prostate biopsy. Variables that predicted prostate cancer included higher PSA level, positive family history of prostate cancer, and abnormal DRE result, whereas a previous negative prostate biopsy was associated with reduced risk. Neither age at biopsy nor PSA velocity contributed independent prognostic information. Higher PSA level, abnormal DRE result, older age at biopsy, and African American race were predictive for high-grade disease (Gleason score ≥ 7) whereas a previous negative prostate biopsy reduced this risk. **CONCLUSIONS:** This predictive model allows an individualized assessment of prostate cancer risk and risk of high-grade disease for men who undergo a prostate biopsy.

J Natl Cancer Inst. 2006 Apr 19;98(8):529-34

INTERCHANGEABILITY AND DIAGNOSTIC ACCURACY OF TWO ASSAYS FOR TOTAL AND FREE PROSTATE-SPECIFIC ANTIGEN: TWO NOT ALWAYS RELATED ITEMS.

The variation between different PSA assays seems to influence the interpretation of individual PSA values and the clinical decisions about prostate cancer. One reason for this variability could be the different reactivity of antibodies for the various molecular forms of serum PSA; as a result, samples containing the same amount of tPSA but different proportions of fPSA can produce very different values. In this study, serum samples were collected prospectively from 152 consecutive patients referred to 2 institutions (Regional Hospital, Venice, 90 subjects; San Bortolo Hospital, Vicenza, 62 subjects) for PSA elevation and/or symptoms. Serum samples were assessed according to the manufacturers' instructions on the following 2 analyzers: the Immulite 2000 assay (Diagnostic Products Corporation, Los Angeles, USA), which measures tPSA and fPSA, and the ADVIA Centaur (Bayer Diagnostics, Tarrytown, USA), which assays tPSA and cPSA. cPSA values were transformed into fPSA by the equation $fPSA = tPSA - cPSA$. When taking Immulite tPSA and f/tPSA values as 100%, ADVIA Centaur values were 92.6% and 122%, respectively, which means that 20% of patients would be classified differently according to the traditional biopsy cutoff. In conclusion, there are considerable differences between the 2 methods, which could affect clinical decisions.

Int J Biol Markers. 2007 Apr-Jun;22(2):154-8

BIOCHEMICAL (PROSTATE-SPECIFIC ANTIGEN) RELAPSE: AN ONCOLOGIST'S PERSPECTIVE.

Consensus has not been reached on the exact definition of biochemical relapse after prostatectomy; individual institution definitions of relapse after prostatectomy range from consecutively rising prostate-specific antigen (PSA) values of > 0.2 to > 0.6 ng/mL. PSA measurements after radiation are even less predictable. PSA level is a sensitive marker of occult prostate-cancer relapse and provides early notification of recurrence, but a PSA relapse does not equal a clinical relapse or death from prostate cancer. Data are reviewed from retrospective, single-institution trials that have clarified features of PSA relapse after both prostatectomy and radiation, such as the PSA doubling time and the time to the first PSA elevation, which are associated with clinical progression. Various options for treatment of biochemical relapse are also reviewed; these include hormone therapy, combined chemohormonal therapy, alternative medicine and dietary tactics, new agents, and future strategies, such as vaccination. Currently, there is no standard treatment for biochemical failure with proven benefit in terms of quality of life, time to metastases, or survival. Current options include observation for patients with long PSA doubling times or comorbid medical issues and standard or nontraditional hormone therapy or a clinical trial for men who desire early therapy or who have rapid PSA doubling times (< 10 -12 months). Trials combining the early use of chemotherapy with hormone therapy are promising. Patients should be encouraged to enroll in clinical trials to help establish standards of care.

EPCA-2: A HIGHLY SPECIFIC SERUM MARKER FOR PROSTATE CANCER.

OBJECTIVES: To describe the initial assessment of early prostate cancer antigen (EPCA)-2 as a serum marker for the detection of prostate cancer and to examine its sensitivity and specificity. **METHODS:** Serum samples were obtained from 385 men: those with prostate-specific antigen (PSA) levels less than 2.5 ng/mL, PSA levels of 2.5 ng/mL or greater with negative biopsy findings, benign prostatic hyperplasia, organ-confined prostate cancer, non-organ-confined disease, and prostate cancer with PSA levels less than 2.5 ng/mL. In addition, a diverse group of controls was assessed with an enzyme-linked immunosorbent assay to detect an epitope of the EPCA-2 protein, EPCA-2.22. **RESULTS:** Using a cutoff of 30 ng/mL, the EPCA-2.22 assay had a 92% specificity (95% confidence interval 85% to 96%) for healthy men and men with benign prostatic hyperplasia and 94% sensitivity (95% confidence interval [CI] 93% to 99%) for overall prostate cancer. The specificity for PSA in these selected groups of patients was 65% (95% CI 55% to 75%). Additionally, EPCA-2.22 was highly accurate in differentiating between localized and extracapsular disease (area under the curve 0.89, 95% CI 0.82 to 0.97, $P < 0.0001$) in contrast to PSA (area under the curve 0.62, 95% CI 0.50 to 0.75, $P = 0.05$). **CONCLUSIONS:** The results of our study have shown that EPCA-2 is a novel biomarker associated with prostate cancer that has high sensitivity and specificity and accurately differentiates between men with organ-confined and non-organ-confined disease.

Urology. 2007 Apr;69(4):714-20

THE INFLUENCE OF FINASTERIDE ON THE DEVELOPMENT OF PROSTATE CANCER.

BACKGROUND: Androgens are involved in the development of prostate cancer. Finasteride, an inhibitor of 5 α -reductase, inhibits the conversion of testosterone to dihydrotestosterone, the primary androgen in the prostate, and may reduce the risk of prostate cancer. **METHODS:** In the Prostate Cancer Prevention Trial, we randomly assigned 18,882 men 55 years of age or older with a normal digital rectal examination and a prostate-specific antigen (PSA) level of 3.0 ng per milliliter or lower to treatment with finasteride (5 mg per day) or placebo for seven years. Prostate biopsy was recommended if the annual PSA level, adjusted for the effect of finasteride, exceeded 4.0 ng per milliliter or if the digital rectal examination was abnormal. It was anticipated that 60 percent of participants would have prostate cancer diagnosed during the study or would undergo biopsy at the end of the study. The primary end point was the prevalence of prostate cancer during the seven years of the study. **RESULTS:** Prostate cancer was detected in 803 of the 4,368 men in the finasteride group who had data for the final analysis (18.4%) and 1,147 of the 4,692 men in the placebo group who had such data (24.4%), for a 24.8% reduction in prevalence over the seven-year period (95% confidence interval, 18.6 to 30.6%; $P < 0.001$). Tumors of Gleason grade 7, 8, 9, or 10 were more common in the finasteride group (280 of 757 tumors

[37.0%], or 6.4 percent of the 4,368 men included in the final analysis) than in the placebo group (237 of 1,068 tumors [22.2%], $P < 0.001$ for the comparison between groups; or 5.1% of the 4,692 men included in the final analysis, $P = 0.005$ for the comparison between groups). Sexual side effects were more common in finasteride-treated men, whereas urinary symptoms were more common in men receiving placebo. **CONCLUSIONS:** Finasteride prevents or delays the appearance of prostate cancer, but this possible benefit and a reduced risk of urinary problems must be weighed against sexual side effects and the increased risk of high-grade prostate cancer. Copyright 2003 Massachusetts Medical Society

N Engl J Med. 2003 Jul 17;349(3):215-24

PHYTOSTEROL COMPOSITION OF NUTS AND SEEDS COMMONLY CONSUMED IN THE UNITED STATES.

Phytosterols were quantified in nuts and seeds commonly consumed in the United States. Total lipid extracts were subjected to acid hydrolysis and then alkaline saponification, and free sterols were analyzed as trimethylsilyl derivatives by capillary GC-FID and GC-MS. Delta5-Avenasterol was quantified after alkaline saponification plus direct analysis of the glucoside. Sesame seed and wheat germ had the highest total phytosterol content (400-413 mg/100 g) and Brazil nuts the lowest (95 mg/100 g). Of the products typically consumed as snack foods, pistachio and sunflower kernel were richest in phytosterols (270-289 mg/100 g). beta-Sitosterol, Delta5-avenasterol, and campesterol were predominant. Campestanol ranged from 1.0 to 12.7 mg/100 g. Only 13 mg/100 g beta-sitosterol was found in pumpkin seed kernel, although total sterol content was high (265 mg/100 g). Phytosterol concentrations were greater than reported in existing food composition databases, probably due to the inclusion of sterol glycosides, which represent a significant portion of total sterols in nuts and seeds.

J Agric Food Chem. 2005 Nov 30;53(24):9436-45

MODULATION OF BLOOD PRESSURE, LIPID PROFILES AND REDOX STATUS IN HYPERTENSIVE PATIENTS TAKING DIFFERENT EDIBLE OILS.

BACKGROUND: Free oxygen radicals and insufficiency of antioxidants have been implicated in the pathogenesis of hypertension. We determined the effect of edible oils on blood pressure, lipid profiles and redox status in hypertensive patients given antihypertensive therapy (nifedipine-calcium channel blocker). **METHODS:** 530 patients medicated with nifedipine were divided into 3 groups (356 patients-sesame oil; 87 patients-sunflower oil; 47 patients-groundnut oil) and the control group (n=40) received only the drug, nifedipine. The respective oils were supplied to the patients and instructed to use as the only edible oil for 60 days, which comes to 35 g of oil/day/person. Blood pressure, lipid profiles [total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and triglycerides (TG)], lipid peroxidation [thiobarbituric acid reactive substances (TBARS)], enzymatic [superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx)] and nonenzymatic [(vitamin C, vitamin E, beta-carotene and reduced glutathione (GSH)] in blood were measured at baseline and after 60 days of oil substitution. **RESULTS:** Patients with nifedipine alone or with respective oils had significantly lowered blood pressure. TC, LDL-C and TG decreased while HDL-C elevated in sesame and sunflower oil groups. Increases of HDL-C and TG were noted in groundnut oil group. TBARS levels reduced in all the groups whereas the reduction was remarkable in sesame oil group. Activities of SOD elevated in the 3 oil groups whereas GPx and CAT increased only in sesame oil group. Levels of vitamin C, vitamin E, beta-carotene and GSH increased in sesame oil group whereas vitamin E and beta-carotene were elevated only in sunflower and groundnut oil groups. GSH increased in drug control group also. **CONCLUSION:** Among the 3 oils, sesame oil offers better protection over blood pressure, lipid profiles and lipid peroxidation and increases enzymatic and nonenzymatic antioxidants.

Clin Chim Acta. 2005 May;355(1-2):97-104

SESAME INGESTION AFFECTS SEX HORMONES, ANTIOXIDANT STATUS, AND BLOOD LIPIDS IN POSTMENOPAUSAL WOMEN.

Sesame ingestion has been shown to improve blood lipids in humans and antioxidative ability in animals. Sesamin, a sesame lignan, was recently reported to be converted by intestinal microflora to enterolactone, a compound with estrogenic activity and also an enterometabolite of flaxseed lignans, which are known to be phytoestrogens. Whether sesame can be a source of phytoestrogens is unknown. This study was designed to investigate the effect of sesame ingestion on blood sex hormones, lipids, tocopherol, and ex vivo LDL oxidation in postmenopausal women. Twenty-six healthy subjects attended, and 24 completed, this randomized, placebo-controlled, crossover study. Half of them consumed 50 g sesame seed powder daily for 5 wk, followed by a 3-wk washout period, then a 5-wk 50-g rice powder placebo period. The other half received the 2 supplements in reverse order. After sesame treatment, plasma total cholesterol (TC), LDL-C, the ratio of LDL-C to HDL-C, thiobarbituric acid reactive substances in oxidized LDL, and serum dehydroepiandrosterone sulfate decreased significantly by 5, 10, 6, 23, and 18%, respectively. The ratio of alpha- and gamma-tocopherol to TC increased significantly by 18 and 73%, respectively. All of these variables differed significantly between the 2 treatments. Serum sex hormone-binding globulin and urinary 2-hydroxyestrone (n = 8) increased significantly by 15 and 72%, respectively, after sesame treatment, and these concentrations tended to differ (P = 0.065 and P = 0.090, respectively) from those after the placebo treatment. These results suggest that sesame ingestion

benefits postmenopausal women by improving blood lipids, antioxidant status, and possibly sex hormone status.

J Nutr. 2006 May;136(5):1270-5

SESAMOL INDUCES NITRIC OXIDE RELEASE FROM HUMAN UMBILICAL VEIN ENDOTHELIAL CELLS.

Sesamol, which is derived from sesame seed lignans, is reportedly an antioxidant. Nitric oxide (NO), the most important vascular relaxing factor, is regulated in the endothelium. In addition, NO is involved in protecting endothelium and has antiatherosclerotic and antithrombotic activities. The endothelium produces NO through the regulation of both endothelial NO synthase (eNOS) expression and activity in endothelial cells. This study sought to investigate the effect of sesamol on NO released from human umbilical vein endothelial cells (HUVEC) and to examine the expression and activity of eNOS. Sesamol induced NO release from endothelial cells in a dose-dependent manner (from 1 to 10 microM), as measured 24 h after treatment; the expression of the eNOS gene at both transcription and translation levels; and NOS activity in endothelial cells. The content of cGMP was also increased by sesamol through NO signaling. The transcription of eNOS induced by sesamol was confirmed through the activation of PI-3 kinase-Akt (protein kinase B) signaling. The results demonstrate that sesamol induces NOS signaling pathways in HUVEC and suggest a role for sesamol in cardiovascular reactivity in vivo.

Lipids. 2005 Sep;40(9):955-61

SESAMIN METABOLITES INDUCE AN ENDOTHELIAL NITRIC OXIDE-DEPENDENT VASORELAXATION THROUGH THEIR ANTIOXIDATIVE PROPERTY-INDEPENDENT MECHANISMS: POSSIBLE INVOLVEMENT OF THE METABOLITES IN THE ANTIHYPERTENSIVE EFFECT OF SESAMIN.

Sesamin, a major lignan in sesame seeds and oil, has been known to lower blood pressure in several types of experimental hypertensive animals. A recent study demonstrated that sesamin metabolites had in vitro radical-scavenging activities. Thus, we determined whether the antioxidative effect of sesamin metabolites modulate the vascular tone and contribute to the in vivo antihypertensive effect of sesamin. We used four demethylated sesamin metabolites: SC-1m (piperitol), SC-1 (demethylpiperitol), SC-2m [(1R,2S,5R,6S)-6-(4-hydroxy-3-methoxyphenyl)-2-(3,4-dihydroxyphenyl)-3,7-dioxabicyclo[3,3,0]octane], and SC-2 [(1R,2S,5R,6S)-2,6-bis(3,4-dihydroxyphenyl)-3,7-dioxabicyclo[3,3,0]octane]. SC-1, SC-2m, and SC-2, but not SC-1m, exhibited potent radical-scavenging activities against the xanthine/xanthine oxidase-induced superoxide production. On the other hand, SC-1m, SC-1, and SC-2m produced endothelium-dependent vasorelaxation in phenylephrine-precontracted rat aortic rings, whereas SC-2 had no effect. The SC-1m- and SC-1-induced vasorelaxations were markedly attenuated by pretreatment with a nitric oxide synthase (NOS) inhibitor, NG-nitro-L-arginine (NOARG), or a soluble guanylate cyclase inhibitor, 1H-[1,2,4]oxadiazolo-[4,3-a]quinoxalin-1-one. Neither SC-1m nor SC-1 changed the expression level of endothelial NOS protein in aortic tissues. The antihypertensive effects of sesamin feeding were not observed in chronically NOARG-treated rats or in deoxycorticosterone acetate-salt-treated endothelial NOS-deficient mice. These findings suggest that the enhancement of endothelium-dependent vasorelaxation induced by sesamin metabolites is one of the important mechanisms of the in vivo antihypertensive effect of sesamin.

J Pharmacol Exp Ther. 2006 Jul;318(1):328-35

DIETARY SESAME SEEDS ELEVATE ALPHA-TOCOPHEROL CONCENTRATION IN RAT BRAIN.

We have previously reported that dietary sesame lignan elevates alpha-tocopherol concentration and decreases lipid peroxidation in tissues and serum of rats fed alpha-tocopherol. In this study, the effect of dietary sesame seeds on alpha-tocopherol concentration and lipid peroxidation in rat brain was examined. In experiment 1, male Wistar rats (4 wk old) were fed a vitamin E-free diet, or a diet containing alpha-tocopherol with or without sesame seeds for 1, 4 and 8 wk. The dietary sesame seeds elevated the alpha-tocopherol and lowered the thiobarbituric acid-reactive substance (TBARS) concentrations in the brain of the rats fed alpha-tocopherol for 4 and 8 wk. The dietary sesame seeds maintained the high alpha-tocopherol concentration in the brain during the experimental period, while the concentration of the rats fed alpha-tocopherol without sesame seeds was lowered after 8 wk. Then, the alpha-tocopherol concentration in various regions of the brain of rats fed a basal level of alpha-tocopherol with sesame seeds was compared with that of rats fed an excess amount of alpha-tocopherol in experiment 2. The alpha-tocopherol concentration in the cerebrum, cerebellum, brain stem and hippocampus of the rats fed 50 mg alpha-tocopherol/kg with sesame seeds was higher than those of the rats fed 500 mg alpha-tocopherol/kg without sesame seeds. These results suggest that the dietary sesame seeds are more useful than the intake of an excess amount of alpha-tocopherol, for maintaining a high alpha-tocopherol concentration and inhibiting lipid peroxidation in the various regions of the rat brain.

J Nutr Sci Vitaminol (Tokyo). 2005 Aug;51(4):223-30

WHOLE SESAME SEED IS AS RICH A SOURCE OF MAMMALIAN LIGNAN PRECURSORS AS WHOLE FLAXSEED.

The mammalian lignans enterolactone and enterodiol, which are produced by the microflora in the colon of humans and animals

from precursors in foods, have been suggested to have potential anticancer effects. This study determined the production of mammalian lignans from precursors in food bars containing 25 g unground whole flaxseed (FB), sesame seed (SB), or their combination (FSB; 12.5 g each). In a randomized crossover study, healthy postmenopausal women supplemented their diets with the bars for 4 wk each separated by 4-wk washout periods, and urinary mammalian lignan excretion was measured at baseline and after 4 wk as a marker of mammalian lignan production. Results showed an increase with all treatments (65.1-81.0 $\mu\text{mol/day}$; $P < 0.0001$), which did not differ among treatments. Lignan excretion with the whole flaxseed was similar to results of other studies using ground flaxseed. An unidentified lignan metabolite was detected after consumption of SB and FSB but not of FB. Thus, we demonstrated for the first time that 1) precursors from unground whole flaxseed and sesame seed are converted by the bacterial flora in the colon to mammalian lignans and 2) sesame seed, alone and in combination with flaxseed, produces mammalian lignans equivalent to those obtained from flaxseed alone.

Nutr Cancer. 2005;52(2):156-65

CHEMOPREVENTIVE EFFECT OF RESVERATROL, SESAMOL, SESAME OIL AND SUNFLOWER OIL IN THE EPSTEIN-BARR VIRUS EARLY ANTIGEN ACTIVATION ASSAY AND THE MOUSE SKIN TWO-STAGE CARCINOGENESIS.

Resveratrol, sesamol, sesame oil and sunflower oil are known natural dietary components with intrinsic cancer chemopreventive potentials. As a part of our study of dietary constituents as potential cancer chemopreventive agents, we have assessed the anti-cancer potentials of these products in the promotion stage of cancer development employing the in vitro Epstein-Barr virus early antigen activation assay induced by the tumor promoter 12-O-tetradecanoylphorbol 13-acetate (TPA). Further, we studied the activities of these compounds in the brine shrimp cytotoxicity assay as well as on the stable 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging bioassay with a view to comparing some of the mechanisms of their anti-cancer activity. Finally, we compared the observed chemoprotective capabilities of the four products in the in vivo 7,12 dimethylbenz(a)anthracene initiated and TPA-promoted mouse skin two-stage carcinogenesis protocols. All the products tested showed a profound inhibitory effect on the Epstein-Barr virus early antigen induction using Raji cells. Comparatively, sesame oil was the most potent followed by sesamol and then resveratrol. Only sesamol and resveratrol showed a remarkable cytotoxic activity in the brine shrimp lethality assays as well as profound free radical scavenging activity in the DPPH bioassay. In both test systems, sesamol exhibited a more remarkable activity than resveratrol while sesame oil and sunflower oil did not exhibit any appreciable activity even at the highest concentrations tested (4000 $\mu\text{g/ml}$). In our in vivo assay at a 50-fold molar ratio to TPA, sesamol offered 50% reduction in mouse skin papillomas at 20 weeks after promotion with TPA. Under an identical molar ratio to TPA, resveratrol offered a 60% reduction in the papillomas in mouse at 20 weeks. Thus sesamol seems to be an almost equally potent chemopreventive agent. Sesame oil and sunflower oil offered 20 and 40% protection, respectively, in the mouse skin tumor model. The anti-oxidant capabilities of these compounds could not solely explain the observed anti-cancer characteristics. Resveratrol is present in grapes. Sesamol, a constituent of sesame oil and sunflower oil are regularly consumed dietary natural products. The observed chemopreventive effect of these products particularly warrants more attention since they already exist in the population with no known adverse effects.

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COMPARATIVE EFFECTS OF FLAXSEED AND SESAME SEED ON VITAMIN E AND CHOLESTEROL LEVELS IN RATS.

Flaxseed and sesame seed both contain more than 40% fat, about 20% protein, and vitamin E, mostly gamma-tocopherol. Furthermore, both contain considerable amounts of plant lignans. However, flaxseed contains 54% alpha-linolenic acid, but sesame seed only 0.6%, and the chemical structures of flaxseed and sesame lignans are different. In this study, we investigated the differential effects of flaxseed and sesame seed on plasma and tissue gamma-tocopherol, TBARS, and cholesterol concentrations. Rats were fed experimental diets for 4 wk: vitamin E-free, (-VE), gamma-tocopherol, flaxseed (FS), sesame seed (SS), flaxseed oil (FO), FO with sesamin (FOS), and defatted flaxseed (DFF). SS and FOS diets induced significantly higher gamma-tocopherol concentrations in plasma and liver compared with FS, FO, and DFF diets. Groups fed FS, FO, and FOS showed lower plasma total cholesterol compared with the SS and DFF groups. Higher TBARS concentrations in plasma and liver were observed in the FS and FO groups but not in the FOS group. These results suggest that sesame seed and its lignans induced higher gamma-tocopherol and lower TBARS concentrations, whereas flaxseed lignans had no such effects. Further, alpha-linolenic acid produced strong plasma cholesterol-lowering effects and higher TBARS concentrations.

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