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ABSTRACTS**Lipid Metabolism Disorders****ASSOCIATION BETWEEN POSTPRANDIAL REMNANT-LIKE PARTICLE TRIGLYCERIDE (RLP-TG) LEVELS AND CAROTID INTIMA-MEDIA THICKNESS (IMT) IN JAPANESE PATIENTS WITH TYPE 2 DIABETES: ASSESSMENT BY MEAL TOLERANCE TESTS (MTT).**

Our study evaluated the relationship between the pathologic changes associated with atherosclerosis, as primarily represented by postprandial remnant-like lipoproteins and carotid intima-media thickness (IMT), in type 2 diabetic patients. Meal tolerance tests (MTT) were performed in 68 patients with type 2 diabetes. The subjects were divided by pre-meal and 2-h postprandial triglyceride (TG) levels into the normotriglyceridemia (NTG) group; the postprandial hypertriglyceridemia (PHTG) group; and the fasting hypertriglyceridemia (FHTG) group. HOMA-R values were significantly higher in the FHTG group than in the NTG group, with the plasma pre-heparin LPL mass and serum adiponectin levels in the FHTG and PHTG groups significantly lower than in the NTG group. One- and two hour postprandial RLP-TG levels were significantly higher in the PHTG group than in the NTG group, while there was no significant difference in postprandial glucose levels between the two groups. The IMT values were significantly higher in both the FHTG and PHTG groups than in the NTG group. Logistics regression analysis of the 1- and 2-h RLP-TG values using IMT as an induced variable showed the odds ratio for high IMT values to be 5.17 ($p < 0.05$) for the 1-h RLP-TG values and 3.01 ($p = 0.105$) for the 2-h RLP-TG values. Our study results suggest that delayed TG metabolism leading to the retention of remnants in type 2 diabetic patients appears to be closely associated with atherosclerosis, and that postprandial hyperlipidemia is an independent risk factor for the early onset of atherosclerosis.

*Endocrine. 2005 Nov;28(2):157-63***POSTPRANDIAL LIPEMIA IN MEN WITH METABOLIC SYNDROME, HYPERTENSIVES AND HEALTHY SUBJECTS.**

BACKGROUND: The metabolic syndrome (MetS), as well as postprandial hypertriglyceridemia, is associated with coronary heart disease. This study aimed to evaluate the postprandial lipemia after oral fat tolerance test (OFTT) in subjects with MetS and compare them to hypertensive (HTN) and healthy subjects. **RESULTS:** OFTT was given to 33 men with MetS (defined by the Adult Treatment Panel III), 17 HTN and 14 healthy men. The MetS group was further divided according to fasting triglycerides (TG) into TG \geq 150 [MetS+TG, (n = 22)] or $<$ 150 mg/dl [MetS-TG (n = 11)], and into those with or without hypertension [MetS+HTN (n = 24), MetS-HTN (n = 9), respectively]. TG concentrations were measured before and at 4, 6 and 8 h after OFTT and the postprandial response was quantified using the area under the curve (AUC) for TG. The postprandial response was significantly higher in MetS compared to HTN and healthy men [AUC (SD) in mg/dl/h; 2534 +/- 1016 vs. 1620 +/- 494 and 1019 +/- 280, respectively, $p < \text{or} = 0.001$]. The TG levels were increased significantly in MetS+TG compared to MetS-TG subjects at 4 ($p = 0.022$), 6 ($p < 0.001$) and 8 hours ($p < 0.001$). The TG were increased significantly in MetS-TG compared to healthy subjects at 4 ($p = 0.011$), 6 ($p = 0.001$) and 8 hours ($p = 0.015$). In linear regression analysis only fasting TG levels were a significant predictor of the AUC (Coefficient B = 8.462, $p < 0.001$). **CONCLUSION:** Fasting TG concentration is the main determinant of postprandial lipemia. However, an exaggeration of TG postprandially was found in normotriglyceridemic MetS and HTN compared to healthy subjects. This suggests that intervention to lower fasting TG levels should be recommended in MetS subjects.

*Lipids Health Dis. 2005 Sep 30;4:21***HYPERINSULINEMIA IS ASSOCIATED WITH INCREASED PRODUCTION RATE OF INTESTINAL APOLIPOPROTEIN B-48-CONTAINING LIPOPROTEINS IN HUMANS.**

OBJECTIVE: Whereas postprandial hyperlipidemia is a well-described feature of insulin-resistant states and type 2 diabetes, no previous studies have examined intestinal lipoprotein production rates (PRs) in relation to hyperinsulinemia or insulin resistance in humans. **METHODS AND RESULTS:** Apolipoprotein B-48 (apoB-48)-containing lipoprotein metabolism was examined in the steady-state fed condition with a 15-hour primed constant infusion of [D3]-l-leucine in 14 nondiabetic men with a broad range of body mass index (BMI) and insulin sensitivity. To examine the relationship between indices of insulin resistance and intestinal lipoprotein PR data were analyzed in 2 ways: by correlation and by comparing apoB-48 PRs in those whose fasting plasma

insulin concentrations were above or below the median for the 14 subjects studied (60 pmol/L). ApoB-48 PR was significantly higher in hyperinsulinemic, insulin-resistant subjects (1.73±0.39 versus 0.88±0.13 mg/kg per day; P<0.05) and correlated with fasting plasma insulin concentrations (r=0.558; P=0.038), despite great heterogeneity in apoB-48 kinetic parameters, particularly among the obese subjects. There was no significant difference in clearance of apoB-48 between the 2 groups, nor was there a significant correlation between apoB-48 fractional clearance rate and fasting insulin or homeostasis model assessment-insulin resistance. CONCLUSIONS: These are the first human data to conclusively demonstrate that intestinal apoB-48-containing triglyceride-rich lipoprotein PR is increased in hyperinsulinemic, insulin-resistant humans. Intestinal lipoprotein particle overproduction is a newly described feature of insulin resistance in humans.

Arterioscler Thromb Vasc Biol. 2006 Jun;26(6):1357-63

POSTPRANDIAL LIPAEMIA INDUCES AN ACUTE DECREASE OF INSULIN SENSITIVITY IN HEALTHY MEN INDEPENDENTLY OF PLASMA NEFA LEVELS.

AIMS/HYPOTHESIS: Typical Western diets cause postprandial lipaemia for 18 h per day. We tested the hypothesis that postprandial lipaemia decreases insulin sensitivity. SUBJECTS, MATERIALS AND METHODS: Employing a randomised crossover design, we administered two types of virtually isocaloric meals to ten healthy volunteers on two separate occasions. The meals (Meals 1 and 2) were both designed to produce a rise in triglycerides, but only Meal 1 generated a rise in NEFA, too. Insulin sensitivity, as quantified by an IVGTT with minimal model analysis, was calculated postabsorptively at 08.00 h and postprandially at 13.00 h, i.e. 3 h after meal ingestion. RESULTS: Triglycerides rose from 0.91±0.31 mmol/l postabsorptively to 2.08±0.70 mmol/l postprandially with Meal 1 (p=0.005) and from 0.92±0.41 to 1.71±0.79 mmol/l with Meal 2 (p=0.005). Neither the triglyceride levels at 13.00 h, nor the post-meal AUCs for triglycerides were statistically different between Meal 1 and Meal 2. NEFA rose from 0.44±0.17 mmol/l postabsorptively to 0.69±0.16 mmol/l postprandially with Meal 1 (p=0.005) and showed no significant change with Meal 2 (0.46±0.31 mmol/l postabsorptively vs 0.36±0.32 mmol/l postprandially, p=0.09). Both the NEFA level at 13.00 h and the post-meal AUC for NEFA were significantly higher after Meal 1 than Meal 2. Compared with the postabsorptive state, insulin sensitivity decreased postprandially after each of the two meals to a comparable degree (Meal 1: -53%, p=0.02; Meal 2: -45%, p=0.005). CONCLUSIONS/INTERPRETATION: Our study reveals a drop in insulin sensitivity during postprandial lipaemia and strongly suggests that decreased insulin sensitivity is brought about by elevated plasma levels of triglyceride-rich lipoproteins independently of plasma NEFA levels.

Diabetologia. 2006 Jul;49(7):1612-8

NUCLEAR MAGNETIC RESONANCE-DETERMINED LIPOPROTEIN SUBCLASS PROFILE IN THE DCCT/EDIC COHORT: ASSOCIATIONS WITH CAROTID INTIMA-MEDIA THICKNESS.

AIMS: To relate nuclear magnetic resonance lipoprotein subclass profiles (NMR-LSP) and other lipoprotein-related factors with carotid intima-media thickness (IMT) in Type 1 diabetes. METHODS: Lipoprotein-related factors were determined in sera (obtained in 1997-1999) from 428 female [age 39 ± 7 years (mean ± SD)] and 540 male (age 40 ± 7 years) Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) participants. NMR quantifies chylomicrons, three very low-density lipoprotein (VLDL) subclasses, intermediate density lipoprotein (IDL), three low-density lipoprotein (LDL) subclasses, two high-density lipoprotein (HDL) subclasses, mean VLDL, LDL and HDL size, and LDL particle concentration. Conventional lipids, ApoA1, ApoB and Lp(a) and in vitro LDL oxidizibility were also measured. IMT was determined (in 1994-1995) using high-resolution B-mode ultrasound. Relationships between IMT and lipoproteins were analysed by multiple linear regression, controlling for age, diabetes-related factors, and cardiovascular disease (CVD) risk factors. RESULTS: IMT associations with lipoproteins were stronger for the internal than the common carotid artery, predominantly involving LDL. Internal carotid IMT was positively (P < 0.05) associated with NMR-based LDL subclasses and particle concentration, and with conventional LDL-cholesterol and ApoB in both genders. Common carotid IMT was associated, in men only, with large VLDL, IDL, conventional LDL cholesterol and ApoB. CONCLUSIONS: NMR-LSP reveals significant associations with carotid IMT in Type 1 diabetic patients, even 4 years after IMT measurement. NMR-LSP may aid early identification of high-risk diabetic patients and facilitate monitoring of interventions. Longer DCCT/EDIC cohort follow-up will yield CVD events and IMT progression, permitting more accurate assessment of pre-morbid lipoprotein profiles as determinants of cardiovascular risk in Type 1 diabetes.

Diabet Med. 2006 Sep;23(9):955-66

ENDOTHELIAL DYSFUNCTION INDUCED BY POSTPRANDIAL LIPEMIA IS NEUTRALIZED BY ADDITION OF PROTEINS TO THE FATTY MEAL.

BACKGROUND: Postprandial lipemia is known to reduce endothelium-dependent flow-mediated vasodilation (FMD). Because postprandial lipemia can be acutely mitigated when proteins are added to the fatty meal, we investigated whether this mitigation could neutralize the lipemia-induced endothelial dysfunction. DESIGN: Sixteen healthy students (aged 19-23, eight males and eight females) received three different test meals at intervals of 1 week between successive tests. Each meal contained whipping cream alone or whipping cream together with either caseinate or soy protein. The whipping cream contained 33% fat, and 3 ml (=

1 g fat) was given per kg body weight. The proteins added were either 50 g sodium caseinate or 50 g soy protein. FMD was assessed by two-dimensional ultrasonography of the brachial artery in the fasting state and 1, 2, 3, 4, 5, 6, 7, and 8h after the fatty meal. Blood was withdrawn at the same time-points from the other arm. Triglycerides, free fatty acids, and insulin were determined using routine methods, and both L-arginine and asymmetric dimethylarginine (ADMA) were determined by LC-MS. RESULTS: Postprandial lipemia reduced FMD, the reduction reaching a maximum of 58% after 3 h. This impairment of endothelial function was not observed when either of the test proteins had been added to the fatty meal ($p < 0.01$ for caseinate and $p < 0.001$ for soy protein). The effects of the protein addition were decreases in triglycerides and free fatty acids, increased insulin concentrations at all time-points, and an increased arginine/ADMA ratio between 1 and 5h after the meal, particularly in the case of the soy protein. CONCLUSION: We suggest that the neutralization of the lipemia-induced endothelial dysfunction is caused by direct and indirect effects of the proteins insulinotropy and, secondly, by an increased supply of L-arginine.

Atherosclerosis. 2006 Apr;185(2):313-9

PRESCRIBING AEROBIC EXERCISE FOR THE REGULATION OF POSTPRANDIAL LIPID METABOLISM : CURRENT RESEARCH AND RECOMMENDATIONS.

Prolonged presence of elevated plasma triglycerides (TGs) during the postprandial period has been suggested to increase the risk for coronary artery disease. Aerobic exercise attenuates postprandial lipaemia and this has generally been described as a short-term effect of the exercise. Effects of exercise on postprandial lipaemia have mostly been investigated, and documented, with large exercise-induced energy expenditures (i.e. 1000 kcal). The exact mechanisms involved in the attenuation of postprandial lipaemia with exercise are not completely understood, but it appears that at least two mechanisms are involved: a decrease in TG secretion by the liver and an increase in plasma TG clearance by the muscle. Changes in the metabolism of other lipids, such as those in high-density lipoprotein cholesterol, have been documented only when the exercise is performed some hours before the fat meal. Although factors such as the physical fitness and percentage body fat of an individual are likely to also be involved, the most important factors determining the magnitude of the attenuation in postprandial lipaemia appear to be the magnitude of the exercise-induced energy expenditure and the intensity of exercise. To date, the evidence suggests that healthy individuals can generally induce favourable changes in postprandial lipaemia with aerobic exercise that: (i) is completed during the period extending from 16 hours before a meal through 1.5 hours after a meal; (ii) is of moderate intensity; and (iii) results in an energy expenditure of approximately 500 kcal (or more).

Sports Med. 2006;36(7):547-60

LIPOPROTEIN REMNANTS AND ENDOTHELIAL DYSFUNCTION IN THE POSTPRANDIAL PHASE.

The objective of this work was to study whether changes in remnant lipoprotein (RLP) plasma levels during the postprandial phase relate to alterations of the endothelial function. Fasted patients (15 moderately dyslipidemic men) were given an oral fat load (OFL), and blood samples were collected before the OFL ingestion (T0) and 2, 4, 6, and 8 h (T2, T4, T6, T8) thereafter. Endothelial function, determined as flow-mediated dilatation (FMD) of the brachial artery, was assessed at the same time points. Triglyceridemia peaked between T4 (5.48 +/- 0.64 mmol/liter) and T6 (5.34 +/- 0.89 mmol/liter) and decreased at 8 h (4.36 +/- 0.87 mmol/liter) after the OFL. FMD decreased significantly 6 h after the OFL consumption (from 16.03 +/- 1.32% to 11.53 +/- 1.42%, $P < 0.01$). Cholesterol in RLPs increased steadily up to 6 h and decreased at 8 h (T0 0.53 +/- 0.10, T6 0.81 +/- 0.11, T8 0.73 +/- 0.13 mmol/liter). Fasting levels of triglycerides and cholesterol-RLPs (C-RLPs) correlated significantly with FMD at baseline. The decrease in endothelial function at 6 h also significantly correlated with the area under the curve of triglycerides ($R = 0.53$, $P = 0.04$). Postprandial C-RLPs (area under the curve), however, showed the best correlation with the decrease of FMD ($R = 0.63$, $P = 0.012$). The correlation persisted in a multivariate analysis. We concluded that C-RLPs contribute significantly to the endothelial dysfunction occurring during the postprandial lipemia.

J Clin Endocrinol Metab. 2004 Jun;89(6):2946-50

POSTPRANDIAL LIPEMIA AND CARDIOVASCULAR DISEASE.

Postprandial lipemia, characterized by a rise in triglyceride-rich lipoproteins after eating, is a dynamic, nonsteady-state condition in which humans spend the majority of time. There are several lines of evidence suggesting that postprandial lipemia increases risk of atherogenesis. Clinical data show a correlation between postprandial lipoproteins and the presence/progression of coronary artery disease and carotid intimal thickness. Mechanistic studies demonstrate that triglyceride-rich lipoprotein remnants may have adverse effects on endothelium and can penetrate into the subendothelial space. Exchange of core lipids between postprandial lipoproteins and low-density lipoprotein (LDL)/high-density lipoprotein (HDL) is increased during prolonged lipemia, resulting in small, dense LDL particles and reduced HDL cholesterol levels. Hemostatic variables, including clotting factors, platelet reactivity, and monocyte cytokine expression, may be increased during postprandial lipemia. Collectively, these data suggest that assessment and treatment of atherosclerosis should include parameters related to postprandial lipemia.

Curr Atheroscler Rep. 2003 Nov;5(6):437-44

EARLY ALTERATIONS IN THE POST-PRANDIAL VLDL1 APOB-100 AND APOB-48 METABOLISM IN MEN WITH STRONG HEREDITY FOR TYPE 2 DIABETES.

OBJECTIVES: To study the postprandial triglyceride-rich lipoprotein (TRL) metabolism, specifically the concentrations of very low-density lipoproteins (VLDL); from intestine (apoB-48) and liver (apoB-100), in men with normal fasting triglycerides but at increased risk of developing type 2 diabetes. **DESIGN:** Cross-sectional study. **SUBJECTS AND SETTINGS:** Sixteen healthy men with at least two first-degree relatives with type 2 diabetes were individually matched with 16 control subjects without known diabetes heredity for: age, body mass index, and fasting triglyceride level. They underwent an 8-h meal tolerance test (919 kcal, 51 g fat) during which lipoproteins were separated by density gradient ultracentrifugation. They were characterized by euglycaemic hyperinsulinaemic clamp, peak VO_2 , 7-day diet registration and computed tomography. **RESULTS:** The relatives were, as expected, more insulin resistant than the controls and had increased concentration of postprandial VLDL1 particles (49% higher for VLDL1 apoB-48, $P = 0.04$ and 21% higher for VLDL1 apoB-100, $P = 0.048$). The elevation was related to insulin sensitivity, but not to lifestyle and body composition. Moreover, the concentration of postprandial triglycerides in VLDL1 fraction was inversely related to low-density lipoprotein (LDL) size in both relatives ($r_s = -0.60$, $P = 0.03$) and controls ($r_s = -0.72$, $P = 0.004$). There were no differences in the concentration of triglycerides or apoB-48 and apoB-100 particles in the other fractions (plasma, chylomicron or VLDL2). **CONCLUSION:** Increased postprandial concentration of TRLs in the VLDL1 fraction seems to be present at an early stage in the development of diabetes and probably contributes to the excess risk of future coronary events in insulin-resistant men.

J Intern Med. 2004 Feb;255(2):273-9

AN ACTIVE INGREDIENT OF CAT'S CLAW WATER EXTRACTS IDENTIFICATION AND EFFICACY OF QUINIC ACID.

Historic medicinal practice has defined Cat's Claw, also known as Una de Gato or *Uncaria tomentosa*, as an effective treatment for several health disorders including chronic inflammation, gastrointestinal dysfunction such as ulcers, tumors and infections. The efficacy of Cat's Claw was originally believed, as early as the 1960s, to be due to the presence of oxindole alkaloids. However, more recently water-soluble Cat's Claw extracts were shown not to contain significant amounts of alkaloids (<0.05%), and yet still were shown to be very efficacious. Here we characterize the active ingredients of a water-soluble Cat's Claw extract called C-Med-100 as inhibiting cell growth without cell death thus providing enhanced opportunities for DNA repair, and the consequences thereof, such as immune stimulation, anti-inflammation and cancer prevention. The active ingredients were chemically defined as quinic acid esters and could also be shown to be bioactive in vivo as quinic acid.

J Ethnopharmacol. 2005 Jan 15;96(3):577-84

ANTIOXIDANT ACTIVITY OF ETHANOLIC AND AQUEOUS EXTRACTS OF UNCARIA TOMENTOSA (WILLD.) DC.

The antioxidant properties of aqueous and ethanolic extracts of the *Uncaria tomentosa* bark were evaluated. The analysis included trolox equivalent antioxidant capacity (TEAC), peroxy radical-trapping capacity (PRTC), superoxide radical scavenging activity (SOD) and quantitation of total tannins (TT) and total phenolic compounds (TPC). The obtained results indicate high antioxidant capacity of the studied materials in comparison to the other extracts of fruits, vegetables, cereals and medicinal plants. Higher antioxidant activity and total phenolic compounds of the alcoholic preparations -- TEAC=0.57 mmol of Trolox/g, PRTC=0.52 mmol of Trolox/g and SOD=0.39 U/mg than of the aqueous preparation -- TEAC=0.34 mmol of Trolox/g, PRTC=0.19 mmol of Trolox/g and SOD=0.10 U/mg were observed. These results might suggest higher medical suitability of alcoholic extracts. However, the highly elevated level of tannins in alcoholic extracts may cause undesirable gastric effects.

J Ethnopharmacol. 2006 Mar 8;104(1-2):18-23

A WATER SOLUBLE EXTRACT FROM UNCARIA TOMENTOSA (CAT'S CLAW) IS A POTENT ENHANCER OF DNA REPAIR IN PRIMARY ORGAN CULTURES OF HUMAN SKIN.

Cat's Claw (*Uncaria tomentosa*) water extracts, essentially free of oxindole alkaloids, have been shown to possess a broad spectrum of biological activity including DNA repair enhancement and antiinflammatory properties. These two biological mechanisms are key molecular targets to develop treatments that protect skin exposed to ultraviolet light from the sun. Because C-Med-100, a Cat's Claw water extract, is the only documented natural source of components that can up-regulate simultaneously both DNA repair and antiinflammation, its ability to modulate DNA repair in human skin organ cultures was undertaken. For this purpose skin cultures were treated with or without 5 mg/mL C-Med-100, irradiated with 0-100 mJ/cm² UVB, and microscopically analysed for necrosis as well as the level of pyrimidine dimers using immunofluorescent TT-dimer antibody staining. The data clearly demonstrated that co-incubation with C-Med-100 reduced skin cell death from UV exposure, and this protection was accounted for by a concomitant increase in DNA repair. Based on these results, it was concluded that C-Med-100 was a natural plant extract worthy of further consideration as a sunscreen product.

Phytother Res. 2006 Mar;20(3):178-83

MODULATION OF CYTOKINE EXPRESSION BY TRADITIONAL MEDICINES: A REVIEW OF HERBAL IMMUNOMODULATORS.

Modulation of cytokine secretion may offer novel approaches in the treatment of a variety of diseases. One strategy in the modulation of cytokine expression may be through the use of herbal medicines. A class of herbal medicines, known as immunomodulators, alters the activity of immune function through the dynamic regulation of informational molecules such as cytokines. This may offer an explanation of the effects of herbs on the immune system and other tissues. For this informal review, the authors surveyed the primary literature on medicinal plants and their effects on cytokine expression, taking special care to analyze research that utilized the multi-component extracts equivalent to or similar to what are used in traditional medicine, clinical phytotherapy, or in the marketplace. METHODOLOGY: MEDLINE, EBSCO, and BIOSIS were used to identify research on botanical medicines, in whole or standardized form, that act on cytokine activity through different models, i.e., in vivo

(human and animal), ex vivo, or in vitro. RESULTS: Many medicinal plant extracts had effects on at least one cytokine. The most frequently studied cytokines were IL-1, IL-6, TNF, and IFN. *Acalypha wilkesiana*, *Acanthopanax gracilistylus*, *Allium sativum*, *Ananus comosus*, *Cissampelos sympodialis*, *Coriolus versicolor*, *Curcuma longa*, *Echinacea purpurea*, *Grifola frondosa*, *Harpagophytum procumbens*, *Panax ginseng*, *Polygala tenuifolia*, *Poria cocos*, *Silybum marianum*, *Smilax glabra*, *Tinospora cordifolia*, *Uncaria tomentosa*, and *Withania somnifera* demonstrate modulation of multiple cytokines. CONCLUSION: The in vitro and in vivo research demonstrates that the reviewed botanical medicines modulate the secretion of multiple cytokines. The reported therapeutic success of these plants by traditional cultures and modern clinicians may be partially due to their effects on cytokines. Phytotherapy offers a potential therapeutic modality for the treatment of many differing conditions involving cytokines. Given the activity demonstrated by many of the reviewed herbal medicines and the increasing awareness of the broad-spectrum effects of cytokines on autoimmune conditions and chronic degenerative processes, further study of phytotherapy for cytokine-related diseases and syndromes is warranted.

Altern Med Rev. 2006 Jun;11(2):128-50

INNATE IMMUNE RECOGNITION AND SUPPRESSION OF TUMORS.

In this chapter, we first summarized the strong evidence that now supports the existence of an effective cancer immune surveillance process that prevents cancer development in both mice and humans. We then focused the remainder of the chapter on methods of tumor recognition that contribute to natural host immune suppression of tumors. In particular, NKG2D is a type II transmembrane-anchored glycoprotein expressed as a disulfide-linked homodimer on the surface of all mouse and human natural killer cells (NK cells). Stimulation of NK cell through NKG2D triggers cell-mediated cytotoxicity and in some cases induces production of cytokines. NKG2D binds to family of ligands with structural homology to major histocompatibility complex (MHC) class I, however, NKG2D ligands often display upregulated surface expression on stressed cells and are frequently overexpressed by tumors unlike conventional MHC class I molecules. Evidence clearly implicate that NKG2D recognition plays an important role in tumor immune surveillance.

Adv Cancer Res. 2006;95:293-322

OXINDOLE ALKALOIDS FROM UNCARIA TOMENTOSA INDUCE APOPTOSIS IN PROLIFERATING, G0/G1-ARRESTED AND BCL-2-EXPRESSING ACUTE LYMPHOBLASTIC LEUKAEMIA CELLS.

Natural products are still an untapped source of promising lead compounds for the generation of antineoplastic drugs. Here, we investigated for the first time the antiproliferative and apoptotic effects of highly purified oxindole alkaloids, namely isopteropodine (A1), pteropodine (A2), isomitraphylline (A3), uncarine F (A4) and mitraphylline (A5) obtained from *Uncaria tomentosa*, a South American Rubiaceae, on human lymphoblastic leukaemia T cells (CCRF-CEM-C7H2). Four of the five tested alkaloids inhibited proliferation of acute lymphoblastic leukaemia cells. Furthermore, the antiproliferative effect of the most potent alkaloids pteropodine (A2) and uncarine F (A4) correlated with induction of apoptosis. After 48 h, 100 micromol/l A2 or A4 increased apoptotic cells by 57%. CEM-C7H2 sublines with tetracycline-regulated expression of bcl-2, p16ink4A or constitutively expressing the cowpox virus protein crm-A were used for further studies of the apoptosis-inducing properties of these alkaloids. Neither overexpression of bcl-2 or crm-A nor cell-cycle arrest in G0/G1 phase by tetracycline-regulated expression of p16INK4A could prevent alkaloid-induced apoptosis. Our results show the strong apoptotic effects of pteropodine and uncarine F on acute leukaemic lymphoblasts and recommend the alkaloids for further studies in xenograft models.

Br J Haematol. 2006 Mar;132(5):615-22

THE ANTIPROLIFERATIVE EFFECTS OF UNCARIA TOMENTOSA EXTRACTS AND FRACTIONS ON THE GROWTH OF BREAST CANCER CELL LINE.

Uncaria tomentosa, also known as "Una de gato", is a Rubiaceae species widely used in South-American folk medicine for the treatment of cancer, arthritis, gastritis and epidemic diseases. Extracts of the plant have been shown to possess cytostatic and anti-inflammatory activity as well as mutagenic and antimutagenic properties. However, to date no studies have been carried out to verify the direct antitumor activity of the extracts. The present study investigates the effects of some extracts and their chromatographic fractions from the bark of *U. tomentosa* on the growth of a human breast cancer cell line (MCF7). Our data indicated that, in addition to the antimutagenic activity, *U. tomentosa* extracts and fractions exert a direct antiproliferative activity on MCF7. The bioassay-directed fractionation from barks and leaves resulted in the isolation of two active fractions, which displayed an IC50 of 10 mg/ml and 20 mg/ml, respectively and an antiproliferative effect, with about 90% of inhibition at a concentration of 100 mg/ml.

Anticancer Res. 2001 Jul-Aug;21(4A):2457-61

DNA REPAIR ENHANCEMENT OF AQUEOUS EXTRACTS OF UNCARIA TOMENTOSA IN A HUMAN VOLUNTEER STUDY.

The *Uncaria tomentosa* water extracts (C-Med-100) have been shown to enhance DNA repair, mitogenic response and leukocyte recovery after chemotherapy-induced DNA damage in vivo. In this study, the effect of C-Med-100 supplement was evaluated in a human volunteer study. Twelve apparently healthy adults working in the same environment were randomly assigned into 3 groups with age and gender matched. One group was daily supplemented with a 250 mg tablet containing an aqueous extract of *Uncaria tomentosa* of C-Med-100, and another group with a 350 mg tablet, for 8 consecutive weeks. DNA repair after induction of DNA damage by a standard dose of hydrogen peroxide was measured 3 times before supplement and 3 times after the supplement for the last 3 weeks of the 8 week-supplement period. There were no drug-related toxic responses to C-Med-100 supplement when judged in terms of clinical symptoms, serum clinical chemistry, whole blood analysis and leukocyte differential counts. There was a statistically significant decrease of DNA damage and a concomitant increase of DNA repair in the supplement groups (250 and 350 mg/day) when compared with non-supplemented controls ($p < 0.05$). There was also an increased tendency of PHA induced lymphocyte proliferation in the treatment groups. Taken together, this trial has confirmed the earlier results obtained in the rat model when estimating DNA repair enhancement by C-Med-100.

Phytomedicine. 2001 Jul;8(4):275-82

AN EXTRACT OF UNCARIA TOMENTOSA INHIBITING CELL DIVISION AND NF-KAPPA B ACTIVITY WITHOUT INDUCING CELL DEATH.

Previous reports have demonstrated that extracts of the plant *Uncaria tomentosa* inhibit tumor cell proliferation and inflammatory responses. We have confirmed that C-Med 100, a hot water extract of this plant, inhibits tumor cell proliferation albeit with variable efficiency. We extend these findings by showing that this extract also inhibits proliferation of normal mouse T and B lymphocytes and that the inhibition is not caused by toxicity or by induction of apoptosis. Further, the extract did not interfere with IL-2 production nor IL-2 receptor signaling. Since there was no discrete cell cycle block in C-Med 100-treated cells, we propose that retarded cell cycle progression caused the inhibition of proliferation. Collectively, these data suggested interference with a common pathway controlling cell growth and cell cycle progression. Indeed, we provide direct evidence that C-Med 100 inhibits nuclear factor kappa B (NF-kappa B) activity and propose that this at least partially causes the inhibition of proliferation.

Int Immunopharmacol. 2003 Dec;3(13-14):1889-900

EFFICACY AND SAFETY OF FREEZE-DRIED CAT'S CLAW IN OSTEOARTHRITIS OF THE KNEE: MECHANISMS OF ACTION OF THE SPECIES UNCARIA GUIANENSIS.

AIM: The purpose of this investigation was to evaluate the ability of cat's claw, an Amazonian medicinal plant, to treat osteoarthritis of the knee, collect safety and tolerance information and compare the antioxidant, and anti-inflammatory actions of *Uncaria guianensis* and *Uncaria tomentosa* in vitro. MATERIALS AND METHODS: Forty-five patients with osteoarthritis of the knee were recruited, 30 were treated with freeze-dried *U. guianensis*, and 15 with placebo. Hematological parameters were assessed on entry and exit of the four-week trial. Pain, medical and subject assessment scores and adverse effects were collected at weeks 1, 2 and 4. The antioxidant and anti-inflammatory activity of the cat's claw species was determined by the alpha,alpha-diphenyl-beta-picrylhydrazyl (DPPH) free radical scavenging method. Inhibition of TNFalpha and prostaglandin E2 (PGE2) production was determined in RAW 264.7 cells by ELISA. RESULTS: Cat's claw had no deleterious effects on blood or liver function or other significant side-effects compared to placebo. Pain associated with activity, medical and patient assessment scores were all significantly reduced, with benefits occurring within the first week of therapy. Knee pain at rest or at night, and knee circumference were not significantly reduced by cat's claw during this brief trial. In vitro tests indicated that *U. guianensis* and *U. tomentosa* were equivalent at quenching DPPH radicals (EC50, 13.6-21.7 microg/ml) as well as inhibiting TNFalpha production. However, the latter action was registered at much lower concentrations (EC50, 10.2-10.9 ng/ml). Cat's claw (10 microg/ml) had no effect on basal PGE2 production, but reduced LPS-induced PGE2 release ($P < 0.05$), but at higher concentrations than that required for TNFalpha inhibition. CONCLUSION: Cat's claw is an effective treatment for osteoarthritis. The species, *U. guianensis* and *U. tomentosa* are equiactive. They are effective antioxidants, but their anti-inflammatory properties may result from their ability to inhibit TNFalpha and to a lesser extent PGE2 production.

Inflamm Res. 2001 Sep;50(9):442-8

EFFICACY AND TOLERABILITY OF BOSWELLIA SERRATA EXTRACT IN TREATMENT OF OSTEOARTHRITIS OF KNEE—A RANDOMIZED DOUBLE BLIND PLACEBO CONTROLLED TRIAL.

Osteoarthritis is a common, chronic, progressive, skeletal, degenerative disorder, which commonly affects the knee joint. *Boswellia serrata* tree is commonly found in India. The therapeutic value of its gum (guggulu) has been known. It possesses good anti-inflammatory, anti-arthritis and analgesic activity. A randomized double blind placebo controlled crossover study was conducted to assess the efficacy, safety and tolerability of *Boswellia serrata* Extract (BSE) in 30 patients of osteoarthritis of knee, 15 each receiving active drug or placebo for eight weeks. After the first intervention, washout was given and then the groups were crossed over to receive the opposite intervention for eight weeks. All patients receiving drug treatment reported decrease in knee pain, increased knee flexion and increased walking distance. The frequency of swelling in the knee joint was decreased. Radiologically there was no change. The observed differences between drug treated and placebo being statistically significant, are clinically relevant. BSE was well tolerated by the subjects except for minor gastrointestinal ADRs. BSE is recommended in the patients of osteoarthritis of the knee with possible therapeutic use in other arthritis.

Phytomedicine. 2003 Jan;10(1):3-7

DIETARY SUPPORT WITH BOSWELLIA RESIN IN CANINE INFLAMMATORY JOINT AND SPINAL DISEASE.

An open multi-centre veterinary clinical trial, comparing conditions before and after treatment with a herbal dietary supplement consisting of a natural resin extract of *Boswellia serrata*, was conducted by 10 practicing veterinarians in Switzerland. This traditional plant-based supplement is known for its anti-rheumatic and anti-inflammatory properties. 29 dogs with manifestations of chronic joint and spinal disease were enrolled. Osteoarthritis and degenerative conditions were confirmed radiologically in 25 of 29 cases. The resin extract (BSB108, product of Bogar AG) was administered with the regular food at a dose of 400 mg/10 kg body weight once daily for 6 weeks. Already after two weeks of treatment, an overall efficacy of the dietary supplement was evident in 71% of 24 eligible dogs. A statistically significant reduction of severity and resolution of typical clinical signs in individual animals, such as intermittent lameness, local pain and stiff gait, were reported after 6 weeks. Effects of external factors that aggravate lameness, such as "lameness when moving" and "lameness after a long rest" diminished gradually. In 5 dogs, reversible brief episodes of diarrhea and flatulence occurred, but only once was a relationship to the study preparation suspected. Because quality and stability of the resin extract were ensured, these data suggest that a standardized preparation can be recommended as a herbal dietary supplement providing symptomatic support in canine osteoarthritic disease.

Schweiz Arch Tierheilkd. 2004 Feb;146(2):71-9

HUMAN GENOME SCREEN TO IDENTIFY THE GENETIC BASIS OF THE ANTI-INFLAMMATORY EFFECTS OF BOSWELLIA IN MICROVASCULAR ENDOTHELIAL CELLS.

Inflammatory disorders represent a substantial health problem. Medicinal plants belonging to the Burseraceae family, including *Boswellia*, are especially known for their anti-inflammatory properties. The gum resin of *Boswellia serrata* contains boswellic acids, which inhibit leukotriene biosynthesis. A series of chronic inflammatory diseases are perpetuated by leukotrienes. Although *Boswellia* extract has proven to be anti-inflammatory in clinical trials, the underlying mechanisms remain to be characterized. TNF alpha represents one of the most widely recognized mediators of inflammation. One mechanism by which TNFalpha causes inflammation is by potently inducing the expression of adhesion molecules such as VCAM-1. We sought to test the genetic basis of the antiinflammatory effects of BE (standardized *Boswellia* extract, 5-Loxin) in a system of TNF alpha-induced gene expression in human microvascular endothelial cells. We conducted the first whole genome screen for TNF alpha-inducible genes in human microvascular cells (HMEC). Acutely, TNF alpha induced 522 genes and downregulated 141 genes in nine out of nine pairwise comparisons. Of the 522 genes induced by TNF alpha in HMEC, 113 genes were clearly sensitive to BE treatment. Such genes directly related to inflammation, cell adhesion, and proteolysis. The robust BE-sensitive candidate genes were then subjected to further processing for the identification of BE-sensitive signaling pathways. The use of resources such as GenMAPP, KEGG, and gene ontology led to the recognition of the primary BE-sensitive TNF alpha-inducible pathways. BE prevented the TNF alpha-induced expression of matrix metalloproteinases. BE also prevented the inducible expression of mediators of apoptosis. Most strikingly, however, TNF alpha-inducible expression of VCAM-1 and ICAM-1 were observed to be sensitive to BE. Realtime PCR studies showed that while TNF alpha potently induced VCAM-1 gene expression, BE completely prevented it. This result confirmed our microarray findings and built a compelling case for the anti-inflammatory property of BE. In

an in vivo model of carrageenan-induced rat paw inflammation, we observed a significant antiinflammatory property of BE consistent with our in vitro findings. These findings warrant further research aimed at identifying the signaling mechanisms by which BE exerts its anti-inflammatory effects.

DNA Cell Biol. 2005 Apr;24(4):244-55

INHIBITION BY BOSWELLIC ACIDS OF HUMAN LEUKOCYTE ELASTASE.

Frankincense extracts and boswellic acids, biologically active pentacyclic triterpenes of frankincense, block leukotriene biosynthesis and exert potent anti-inflammatory effects. Screening for additional effects of boswellic acids on further proinflammatory pathways, we observed that acetyl-11-keto-beta-boswellic acid, an established direct, nonredox and noncompetitive 5-lipoxygenase inhibitor, decreased the activity of human leukocyte elastase (HLE) in vitro with an IC50 value of about 15 microM. Among the pentacyclic triterpenes tested in concentrations up to 20 microM, we also observed substantial inhibition by beta-boswellic acid, amyirin and ursolic acid, but not by 18beta-glycyrrhetic acid. The data show that the dual inhibition of 5-lipoxygenase and HLE is unique to boswellic acids: other pentacyclic triterpenes with HLE inhibitory activities (e.g., ursolic acid and amyirin) do not inhibit 5-lipoxygenase, and leukotriene biosynthesis inhibitors from different chemical classes (e.g., NDGA, MK-886 and ZM-230,487) do not impair HLE activity. Because leukotriene formation and HLE release are increased simultaneously by neutrophil stimulation in a variety of inflammation- and hypersensitivity-based human diseases, the reported blockade of two proinflammatory enzymes by boswellic acids might be the rationale for the putative antiphlogistic activity of acetyl-11-keto-beta-boswellic acid and derivatives.

J Pharmacol Exp Ther. 1997 Apr;281(1):460-3

BOSWELLIA CARTERII EXTRACT INHIBITS TH1 CYTOKINES AND PROMOTES TH2 CYTOKINES IN VITRO.

Traditional herbal formulas used to treat inflammatory arthritis in China and India include *Boswellia carterii* or *Boswellia serrata*. They both contain boswellic acids (BAs) which have been shown to exhibit anti-inflammatory and antiarthritic properties. This study tests the hypothesis that mixtures of BAs derived from *B. carterii* have immunomodulatory properties. *B. carterii* plant resin obtained from China was prepared as an ethanol extract, and the presence of seven BAs was confirmed by column chromatography, high-performance liquid chromatography, and UV laser desorption/ionization tandem mass spectroscopy. The extract was then tested for its ability to alter in vitro production of TH1 cytokines (interleukin-2 [IL-2] and gamma interferon) and TH2 cytokines (IL-4 and IL-10) by murine splenocytes. Delivery of the resin extract using ethanol as a solvent resulted in significant cellular toxicity not seen with the addition of ethanol alone. By contrast, delivery of the resin extract using a sesame oil solvent resulted in a dose-dependent inhibition of TH1 cytokines coupled with a dose-dependent potentiation of TH2 cytokines. These results indicate that a purified mixture of BAs from *B. carterii* plant resin exhibits carrier-dependent immunomodulatory properties in vitro.

Clin Diagn Lab Immunol. 2005 May;12(5):575-80

BOSWELLIC ACIDS IN CHRONIC INFLAMMATORY DISEASES.

Oleogum resins from *BOSWELLIA* species are used in traditional medicine in India and African countries for the treatment of a variety of diseases. Animal experiments showed anti-inflammatory activity of the extract. The mechanism of this action is due to some boswellic acids. It is different from that of NSAID and is related to components of the immune system. The most evident action is the inhibition of 5-lipoxygenase. However, other factors such as cytokines (interleukins and TNF-alpha) and the complement system are also candidates. Moreover, leukocyte elastase and oxygen radicals are targets. Clinical studies, so far with pilot character, suggest efficacy in some autoimmune diseases including rheumatoid arthritis, Crohn's disease, ulcerative colitis and bronchial asthma. Side effects are not severe when compared to modern drugs used for the treatment of these diseases.

Planta Med. 2006 Oct;72(12):1100-16

EFFECTS OF BOSWELLIA SERRATA GUM RESIN IN PATIENTS WITH BRONCHIAL ASTHMA: RESULTS OF A DOUBLE-BLIND, PLACEBO-CONTROLLED, 6-WEEK CLINICAL STUDY.

The gum resin of *Boswellia serrata*, known in Indian Ayurvedic system of medicine as *Salai guggal*, contains boswellic acids, which have been shown to inhibit leukotriene biosynthesis. In a double-blind, placebo-controlled study forty patients, 23 males and 17 females in the age range of 18 - 75 years having mean duration of illness, bronchial asthma, of 9.58 +/- 6.07 years were treated with a preparation of gum resin of 300 mg thrice daily for a period of 6 weeks. 70% of patients showed improvement of disease as evident by disappearance of physical symptoms and signs such as dyspnoea, rhonchi, number of attacks, increase in FEV₁, FVC and PEF_r as well as decrease in eosinophilic count and ESR. In the control group of 40 patients 16 males and 24 females in the age range of 14-58 years with mean of 32.95 +/- 12.68 were treated with lactose 300 mg thrice daily for 6

weeks. Only 27% of patients in the control group showed improvement. The data show a definite role of gum resin of *Boswellia serrata* in the treatment of bronchial asthma.

Eur J Med Res. 1998 Nov 17;3(11):511-4

CYTOSTATIC AND APOPTOSIS-INDUCING ACTIVITY OF BOSWELLIC ACIDS TOWARD MALIGNANT CELL LINES IN VITRO.

Boswellic acids from frankincense were identified as the active compounds which inhibit leukotriene biosynthesis, 5-lipoxygenase and exert antiproliferative activity toward a variety of malignant cells. Because of the relevance for the clinical application, we tested the ethanolic extract of *Boswellia serrata* gum resin containing a defined amount of boswellic acids for its cytotoxic, cytostatic and apoptotic activity on five leukemia (HL-60, K 562, U937, MOLT-4, THP-1) and two brain tumor (LN-18, LN-229) cell lines by WST-1 assay and flow cytometry. The *Boswellia serrata* extract induced dose-dependent antiproliferative effects on all human malignant cells tested with GI50 values (extract concentration producing 50% cell growth inhibition) between 57.0 and 124.1 micrograms/ml. In three haematological cell lines (K562, U937, MOLT-4) the effect of total extract expressed in GI50 was 2.8-, 3.3- and 2.3-times more potent ($p < 0.05$) than pure 3-O-acetyl-11-keto-beta-boswellic acid (AKBA). Morphological changes after 24-27 hours and the detection of apoptotic cells by AnnexinV-binding and/or by the detection of propidium iodide-labelled DNA with flow cytometry, confirmed the apoptotic cell death. The results of this study suggest the effectiveness of *Boswellia serrata* extract with defined content of boswellic acids.

Anticancer Res. 2002 Sep-Oct;22(5):2853-62

USE OF COMPLEMENTARY AND ALTERNATIVE MEDICINE IN GERMANY—A SURVEY OF PATIENTS WITH INFLAMMATORY BOWEL DISEASE.

BACKGROUND: Previous studies have suggested an increasing use of complementary and alternative medicine (CAM) in patients with inflammatory bowel disease (IBD). The aim of our study was to evaluate the use of CAM in German patients with IBD. **METHODS:** A questionnaire was offered to IBD patients participating in patient workshops which were organized by a self-help association, the German Crohn's and Colitis Association. The self-administered questionnaire included demographic and disease-related data as well as items analysing the extent of CAM use and satisfaction with CAM treatment. Seven commonly used CAM methods were predetermined on the questionnaire. **RESULTS:** 413 questionnaires were completed and included in the analysis ($n = 153$ male, $n = 260$ female; $n = 246$ Crohn's disease, $n = 164$ ulcerative colitis). 52 % of the patients reported CAM use in the present or past. In detail, homeopathy (55%), probiotics (43%), classical naturopathy (38%), *Boswellia serrata* extracts (36%) and acupuncture/Traditional Chinese Medicine (TCM) (33%) were the most frequently used CAM methods. Patients using probiotics, acupuncture and *Boswellia serrata* extracts (incense) reported more positive therapeutic effects than others. Within the statistical analysis no significant predictors for CAM use were found. 77% of the patients felt insufficiently informed about CAM. **CONCLUSION:** The use of CAM in IBD patients is very common in Germany, although a large proportion of patients felt that information about CAM is not sufficient. However, to provide an evidence-based approach more research in this field is desperately needed. Therefore, physicians should increasingly inform IBD patients about benefits and limitations of CAM treatment.

BMC Complement Altern Med. 2006 May 22;6:19

MECHANISMS UNDERLYING THE ANTI-INFLAMMATORY ACTIONS OF BOSWELLIC ACID DERIVATIVES IN EXPERIMENTAL COLITIS.

Recent clinical trials of the gum resin of *Boswellia serrata* have shown promising results in patients with ulcerative colitis. The objective of this study was to determine whether a semisynthetic form of acetyl-11-keto-beta-boswellic acid (sAKBA), the most potent anti-inflammatory component of the resin, also confers protection in experimental murine colitis induced by dextran sodium sulfate (DSS) to compare its effects with those standard medications of ulcerative colitis like steroids and to examine whether leukocyte-endothelial cell adhesion is a major target of action of sAKBA. Clinical measurements of disease activity and histology were used to assess disease progression, and intravital microscopy was employed to monitor the adhesion of leukocytes and platelets in postcapillary venules of the inflamed colon. sAKBA treatment significantly blunted disease activity as assessed both grossly and by histology. Similarly, the recruitment of adherent leukocytes and platelets into inflamed colonic venules was profoundly reduced in mice treated with sAKBA. Because previous studies in the DSS model have shown that P-selectin mediates these blood cell-endothelial cell interactions, the expression of P-selectin in the colonic microcirculation was monitored using the dual-radiolabeled antibody technique. The treatment of established colitis with sAKBA largely prevented the P-selectin upregulation normally associated with DSS colitis. All of the protective responses observed with sAKBA were comparable to that realized in mice treated with a corticosteroid. Our findings demonstrated an anti-inflammatory effect of sAKBA and indicated that P-selectin-mediated recruitment of inflammatory cells is a major site of action for this novel anti-inflammatory agent.

EFFECT OF HEXANE EXTRACT OF BOSWELLIA SERRATA OLEO-GUM RESIN ON CHEMICALLY INDUCED LIVER DAMAGE.

The hexane extract of oleo-gum-resin of *Boswellia serrata* (BSHE) was evaluated for its effect on liver injury induced by carbon tetrachloride, paracetamol or thioacetamide. The BSHE was given in two different doses (87.5 mg/kg p.o. and 175 mg/kg p.o.). Silymarin, a known hepatoprotective agent was used as standard. The lower dose of BSHE (87.5 mg/kg p.o.) significantly reduced the elevated levels of serum marker enzymes and prevented the increase in liver weight in all three models of liver injury, while the higher dose showed mild hepatoprotective activity. The hepatoprotective effect of lower dose of BSHE was supported by changes in histopathology. It was concluded that hexane extract of oleo-gum-resin of *Boswellia serrata* plant in lower doses possess hepatoprotective activity.

Pak J Pharm Sci. 2006 Apr;19(2):129-33

FOUR NEW NEUROPROTECTIVE DIHYDROPYRANOCOUMARINS FROM ANGELICA GIGAS.

Four new dihydropyrano coumarins were isolated from *Angelica gigas* roots through neuroprotective activity-guided isolation and were characterized as decursinol derivatives 4"-hydroxytigloyldecursinol (1), 4"-hydroxydecursinol (2), (2"S,3"S)-epoxyangeloyldecursinol (3), and (2"R,3"R)-epoxyangeloyldecursinol (4), respectively. All four new dihydropyrano coumarins and major coumarin derivatives of *A. gigas*, decursinol and decursin, exhibited significant protective activity against glutamate-induced neurotoxicity when added to primary cultures of rat cortical cells at concentrations ranging from 0.1 to 10 microM.

J Nat Prod. 2005 Jan;68(1):56-9

POTENT ANTIANDROGEN AND ANDROGEN RECEPTOR ACTIVITIES OF AN ANGELICA GIGAS-CONTAINING HERBAL FORMULATION: IDENTIFICATION OF DECURSIN AS A NOVEL AND ACTIVE COMPOUND WITH IMPLICATIONS FOR PREVENTION AND TREATMENT OF PROSTATE CANCER.

Androgen and androgen receptor (AR)-mediated signaling are crucial for the development of prostate cancer. Identification of novel and naturally occurring phytochemicals that target androgen and AR signaling from Oriental medicinal herbs holds exciting promises for the chemoprevention of this disease. In this article, we report the discovery of strong and long-lasting antiandrogen and AR activities of the ethanol extract of a herbal formula (termed KMKKT) containing Korean *Angelica gigas* Nakai (AGN) root and nine other Oriental herbs in the androgen-dependent LNCaP human prostate cancer cell model. The functional biomarkers evaluated included a suppression of the expression of prostate-specific antigen (PSA) mRNA and protein (IC₅₀, approximately 7 microg/mL, 48-hour exposure) and an inhibition of androgen-induced cell proliferation through G1 arrest and of the ability of androgen to suppress neuroendocrine differentiation at exposure concentrations that did not cause apoptosis. Through activity-guided fractionation, we identified decursin from AGN as a novel antiandrogen and AR compound with an IC₅₀ of approximately 0.4 microg/mL (1.3 micromol/L, 48-hour exposure) for suppressing PSA expression. Decursin also recapitulated the neuroendocrine differentiation induction and G1 arrest actions of the AGN and KMKKT extracts. Mechanistically, decursin in its neat form or as a component of AGN or KMKKT extracts inhibited androgen-stimulated AR translocation to the nucleus and down-regulated AR protein abundance without affecting the AR mRNA level. The novel antiandrogen and AR activities of decursin and decursin-containing herbal extracts have significant implications for the chemoprevention and treatment of prostate cancer and other androgen-dependent diseases.

Cancer Res. 2006 Jan 1;66(1):453-63

BLOCKADE OF NUCLEAR FACTOR-KAPPA B SIGNALING PATHWAY AND ANTI-INFLAMMATORY ACTIVITY OF CARDAMOMIN, A CHALCONE ANALOG FROM ALPINIA CONCHIGERA.

Nuclear factor-kappaB (NF-kappaB) and the signaling pathways that regulate its activity have become a focal point for intense drug discovery and development efforts. NF-kappaB regulates the transcription of a large number of genes, particularly those involved in immune, inflammatory, and antiapoptotic responses. In our search for NF-kappaB inhibitors from natural resources, we identified cardamomin, 2',4'-dihydroxy-6'-methoxychalcone, as an inhibitor of NF-kappaB activation from *Alpinia conchigera* Griff (Zingiberaceae). In present study, we demonstrated the effect of cardamomin on NF-kappaB activation in lipopolysaccharide (LPS)-stimulated RAW264.7 cells and LPS-induced mortality. This compound significantly inhibited the induced expression of NF-kappaB reporter gene by LPS or tumor necrosis factor (TNF)-alpha in a dose-dependent manner. LPS-induced production of TNF-alpha and NO as well as expression of inducible nitric-oxide synthase and cyclooxygenase-2 was significantly suppressed by the treatment of cardamomin in RAW264.7 cells. Also, cardamomin inhibited not only LPS-induced degradation and phosphorylation of inhibitor kappaBalpha (IkappaBalpha) but also activation of inhibitor kappaB (IkappaB) kinases and nuclear translocation of NF-kappaB. Further analyses revealed that cardamomin did not directly inhibit IkappaB kinases, but it significantly suppressed LPS-induced activation of Akt. Moreover, cardamomin suppressed transcriptional activity and phosphorylation of Ser536 of RelA/p65 subunit of NF-kappaB. However, this compound did not inhibit LPS-induced activation of extracellular signal-regulated kinase and stress-activated protein kinase/c-Jun NH(2)-terminal kinase, but significantly impaired activation of p38 mitogen-activated protein kinase. We also demonstrated that pretreatment of cardamomin rescued C57BL/6 mice from LPS-induced mortality in conjunction with decreased serum level of TNF-alpha. Together, cardamomin could be valuable candidate for the intervention of NF-kappaB-dependent pathological condition such as inflammation.

ANTINOCICEPTIVE MECHANISMS OF ORALLY ADMINISTERED DECURSINOL IN THE MOUSE.

Antinociceptive profiles of decursinol were examined in ICR mice. Decursinol administered orally (from 5 to 200 mg/kg) showed an antinociceptive effect in a dose-dependent manner as measured by the tail-flick and hot-plate tests. In addition, decursinol attenuated dose-dependently the writhing numbers in the acetic acid-induced writhing test. Moreover, the cumulative response time of nociceptive behaviors induced by an intraplantar formalin injection was reduced by decursinol treatment during the both 1st and 2nd phases in a dose-dependent manner. Furthermore, the cumulative nociceptive response time for intrathecal (i.t.) injection of TNF-alpha (100 pg), IL-1 beta (100 pg), IFN-gamma (100 pg), substance P (0.7 microg) or glutamate (20 microg) was dose-dependently diminished by decursinol. Intraperitoneal (i.p.) pretreatment with yohimbine, methysergide, cyproheptadine, ranitidine, or 3,7-dimethyl-1-propargylxanthine (DMPX) attenuated inhibition of the tail-flick response induced by decursinol. However, naloxone, thioperamide, or 1,3-dipropyl-8-(2-amino-4-chloro-phenyl)-xanthine (PACPX) did not affect inhibition of the tail-flick response induced by decursinol. Our results suggests that decursinol shows an antinociceptive property in various pain models. Furthermore, antinociception of decursinol may be mediated by noradrenergic, serotonergic, adenosine A(2), histamine H(1) and H(2) receptors.

Life Sci. 2003 Jun 13;73(4):471-85

THE ANTIOXIDATIVE AND IMMUNOSTIMULATING PROPERTIES OF D-GLUCOSAMINE.

The objective of the present study was to investigate the antioxidant activity and immunostimulating property of glucosamine (GlcN) using various in vitro and in vivo tests. Results showed that GlcN possessed excellent antioxidant activities as manifested by strong chelating effect on ferrous ions and protection of macromolecules such as protein, lipid, and deoxyribose from oxidative damage induced by hydroxyl radicals. The immunostimulating effects of GlcN were further evaluated through various immunological tests. GlcN showed excellent activity of enhancing splenocyte proliferation. Neutral red pinocytosis and NO production in mouse peritoneal macrophages were significantly augmented. Oral administration of GlcN to mice for 20 days significantly enhanced the serum antibody level in mice in response to sheep red blood cells (SRBC), increased the relative organ weight of spleen and thymus tissue, and promoted the delayed-type hypersensitivity (DTH) against SRBC as compared with control group. In conclusion, the present investigation reveals GlcN is biologically functional in antioxidative activities and immunostimulating properties.

Int Immunopharmacol. 2007 Jan;7(1):29-35

GLUCOSAMINE LONG-TERM TREATMENT AND THE PROGRESSION OF KNEE OSTEOARTHRITIS: SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS.

OBJECTIVE: To investigate the structural and symptomatic efficacy and safety of glucosamine in knee osteoarthritis (OA). **DATA SOURCES:** Clinical trials of glucosamine were identified through electronic searches (MEDLINE, EMBASE, BIOSIS, EMB review, the Cochrane Library) using the key words glucosamine, osteoarthritis, degenerative joint disease, degenerative arthritis, osteoarthrosis, gonarthrosis, knee, disease progression, and clinical trial. The bibliographic databases were searched from their respective inception dates to August 2004. We also hand-searched reference lists of relevant articles. **STUDY SELECTION AND DATA EXTRACTION:** Studies were included if they were double-blind, randomized, controlled trials that evaluated oral glucosamine long-term treatment in knee OA; lasting at least one year; and reporting as outcome measures the symptom severity and disease progression as assessed by joint space narrowing. Two authors interpreted data independently. Disagreements were resolved through discussion. **DATA SYNTHESIS:** Glucosamine sulfate was more effective than placebo in delaying structural progression in knee OA. The risk of disease progression was reduced by 54% (pooled RR 0.46; 95% CI 0.28 to 0.73; $p = 0.0011$). The number-needed-to-treat was 9 (95% CI 6 to 20). The pooled effect sizes for pain reduction and improvement in physical function were 0.41 (95% CI 0.21 to 0.60; $p < 0.0001$) and 0.46 (95% CI 0.27 to 0.66; $p < 0.0001$), respectively, in favor of glucosamine sulfate. Glucosamine sulfate caused no more adverse effects than placebo. **CONCLUSIONS:** The available evidence suggests that glucosamine sulfate may be effective and safe in delaying the progression and improving the symptoms of knee OA. Due to the sparse data on structural efficacy and safety, further studies are warranted.

Ann Pharmacother. 2005 Jun;39(6):1080-7

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