

Allergies

ABSTRACTS

- Bengtsson A., 2001. Thiols decrease cytokine levels and down-regulate the expression of CD30 on human allergen-specific T helper (Th) 0 and Th2 cells.
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Thiols decrease cytokine levels and down-regulate the expression of CD30 on human allergen-specific T helper (Th) 0 and Th2 cells.

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Clin Exp Immunol 2001 Mar;123(3):350-360

The thiol antioxidant N-acetyl- L-cysteine (NAC), known as a precursor of glutathione (GSH), is used in AIDS treatment trials, as a chemoprotectant in cancer chemotherapy and in treatment of chronic bronchitis. In vitro, GSH and NAC are known to enhance T cell proliferation, production of IL-2 and up-regulation of the IL-2 receptor. The 120-kD CD30 surface antigen belongs to the tumour necrosis factor (TNF) receptor superfamily. It is expressed by activated T helper (Th) cells and its expression is sustained in Th2 cells. We have analysed the effect of GSH and NAC on the cytokine profile and CD30 expression on human allergen-specific T cell clones (TCC). TCC were stimulated with anti-CD3 antibodies in the presence of different concentrations of GSH and NAC. Both thiols caused a dose dependent down-regulation of IL-4, IL-5 and IFN-gamma levels in Th0 and Th2 clones, with the most pronounced decrease of IL-4. Furthermore, they down-regulated the surface expression of CD30, and the levels of soluble CD30 (sCD30) in the culture supernatants were decreased. In contrast, the surface expression of CD28 or CD40 ligand (CD40L) was not significantly changed after treatment with 20 m M NAC. These results indicate that GSH and NAC favour a Th1 response by a preferential down-regulation of IL-4. In addition, the expression of CD30 was down regulated by GSH and NAC, suggesting that CD30 expression is dependent on IL-4, or modified by NAC. In the likely event that CD30 and its soluble counterpart prove to contribute to the pathogenesis in Th2 related diseases such as allergy, NAC may be considered as a future therapeutic agent in the treatment of these diseases.

Is the use of benzalkonium chloride as a preservative for nasal formulations a safety concern? A cautionary note based on compromised mucociliary transport.

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J Allergy Clin Immunol 2000 Jan;105(1 Pt 1):39-44

BACKGROUND: Topical nasal solution and suspension delivery systems are available for short- and long-acting vasoconstrictors, ipratropium, cromolyn, azelastine, and glucocorticosteroids. The use of intranasal glucocorticosteroids has increased substantially because the efficacy of these agents has been well established for the treatment of perennial and seasonal allergic rhinitis. Adverse local effects of burning, irritation, and dryness are occasionally associated with glucocorticosteroid nasal preparations. Benzalkonium chloride (BKC) is a quaternary ammonium antimicrobial agent included in some nasal solutions (including glucocorticosteroids) to prevent the growth of bacteria. Some reports suggest that BKC in nasal sprays may cause adverse effects, including reduced mucociliary transport, rhinitis medicamentosa, and neutrophil dysfunction.

OBJECTIVE: This article summarizes recent literature about possible adverse biologic effects associated with BKC as a nasal spray preservative by examining its effects on the following properties of mucociliary transport: ciliary motion, ciliary form, ciliary beat frequency, electron microscopy, and particle movement/saccharin clearance tests.

CONCLUSION: Both animal and human in vitro data suggest that BKC promotes ciliostasis and reduction in mucociliary transport that may be partially masked by absorption and dilution effects occurring in respiratory mucus. These possible confounding factors may account for several disparate human in vivo results. The use of BKC-free glucocorticosteroid formulations should be considered, particularly in patients who complain of nasal burning, dryness, or irritation.

Effects of Orally consumed aloe vera juice on gastrointestinal function in normal humans

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Preventive Medicine March/April 1985

This study evaluated the effect of oral Aloe Vera juice supplemented on gastric pH, stool specific gravity, protein digestion/absorption, and stool microbiology. Results indicate that supplemental oral Aloe Vera juice is well tolerated by most individuals and has a favorable effects upon a number of gastrointestinal parameters. A discussion of the potential role of Aloe Vera juice on inflammatory bowel disorders based upon this work presented.

Effect of vitamin C on histamine bronchial responsiveness of patients with allergic rhinitis

Bucca C.; Rolla G.; Oliva A.; Farina J.-C. Clinica Medica I, Dpt. Scienz Biomediche e Oncologia Umana, Via Genova3, 10126 Torino Italy

Ann. Allergy (USA), 1990, 65/4 (311-314)

The effect of acute oral administration of 2 g vitamin C on bronchial responsiveness to inhaled histamine in 16 patients with allergic rhinitis was compared with placebo on two consecutive days in double-blind, crossover design. The PC15FEV1 was significantly increased one hour after treatment with vitamin C but not after placebo.

Pretreatment of skin with a Ginkgo biloba extract/sodium carboxymethyl-beta-1,3-glucan formulation appears to inhibit the elicitation of allergic contact dermatitis in man

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Contact Dermatitis (Denmark), 1998, 38/3 (123-126)

The clinical efficiency of mitigating contact dermatitis with a Ginkgo biloba extract and carboxymethyl-beta-1,3-glucan formulation was investigated in a double-blind versus placebo study using 22 subjects (Caucasian women aged 22-55 years) with allergic contact dermatitis from various substances in the European standard series. The formulation was applied to intact skin 2 x a day for 2 weeks ('in use' application) prior to a single application of a selected contact allergen under a Finn Chamber for 24 h. Readings were carried out in a blind study by a dermatologist 2 and 3 days after patch removal. Representative photographs were taken of treated, placebo and untreated test areas. 68.2% of the panelists showed significantly reduced skin reactivity ($p = 0.037^*$) on the treated site 2 days after patch removal, versus untreated and/or placebo sites. This finding indicates that the Ginkgo biloba/carboxymethyl-beta-1,3-glucan formulation can mitigate against allergic contact dermatitis.

The potential role of tocopherol in asthma and allergies: modification of the leukotriene pathway.

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BioDrugs 2001;15(2):81-86

Metabolism of arachidonic acid via the 5-lipoxygenase (5-LO) pathway leads to the formation of hydroperoxyeicosatetraenoic acids (HPETEs) and leukotriene (LT) A₄. This unstable allylic epoxide can be further converted by secondary enzymes into LTB₄ and cysteinyl LTs. LTs represent a family of potent biologically active compounds synthesised by specific cell types and by transcellular biosynthetic mechanisms. Cysteinyl LTs are involved in the pathogenesis of asthma, and recent data indicate that individuals with asthma may have enhanced basal excretion of urinary LTE₄ compared with normal individuals. Tocopherol (vitamin E) and tocopherol acetate strongly inhibit potato 5-LO in an irreversible and noncompetitive way, and, by affecting the redox state of cells possessing 5-LO, they may influence the production of biologically active LTs. It has been reported that normal plasma levels of tocopherol may enhance the lipoxygenation of arachidonic acid, whereas higher tocopherol levels exert a suppressive effect that is consistent with its role as a hydroperoxide scavenger. Receptor-mediated activation of neutrophils in individuals with asthma results in the synthesis of LTs. This activation is inhibited by tocopherol in a concentration-dependent manner. Additional controlled studies are needed to assess the effect of tocopherol on leukotriene production in asthmatic individuals. The results of these studies may be useful in developing new therapeutic approaches in asthmatic/allergic patients.

Increase of intestinal Bifidobacterium and suppression of coliform bacteria with short-term yogurt ingestion.

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J Dairy Sci 1999 Nov;82(11):2308-2314

To determine whether ingestion of yogurt would alter human intestinal bacterial composition and whether Bifidobacterium numbers would increase in the intestine, 34 healthy volunteers were studied. The experimental period was 26 d, including an initial 8 d without yogurt, 10 d with three bottles (230 ml each) of AB yogurt per day (President Enterprise Corporation, Tainan, Taiwan), and 8 d without yogurt. Stool samples were taken at 3- to 4-d intervals. The bacteria of each fresh stool sample were promptly analyzed by dilution and culture on blood, MacConkey, Center for Disease Control and NNLP agars, the agar contained nalidixic acid, neomycin sulfate, LiCl, and paromomycin sulfate for aerobes, coliforms, anaerobes, and bifidobacteria, respectively. The number of bacteria was determined as colony-forming units per gram of dried stool. Results indicated that ingestion of AB yogurt increased the counts of anaerobic bacteria, suppressed aerobic bacteria, and significantly elevated the bifidus to coliform ratio. Arbitrarily primed polymerase chain reaction was used to differentiate the identity of bifidobacteria in four volunteers before and after yogurt ingestion and confirmed that *B. bifidum* ingested from the yogurt survived and proliferated in the stool throughout the experiment. However, the elevated bifidus to coliform ratio gradually diminished and disappeared after yogurt consumption was discontinued. In conclusion, ingestion of yogurt increased the numbers of stool bifidobacteria and suppressed coliform bacteria. The ingested bifidobacteria survived for more than 8 d after yogurt consumption was discontinued.

Influence of glutamine on cytokine production by human gut in vitro.

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Cytokine 2001 Feb 7;13(3):148-154

BACKGROUND: glutamine modulates cytokine production by immune cells in vitro and protects the gut from experimental enterocolitis, but data on the effect of glutamine on cytokine production in human gut are lacking. **AIM:** to assess the effect of glutamine pre-treatment in vivo and in vitro on cytokine production by intestinal mucosa.

METHODS: nine fasted volunteers received either enteral glutamine or saline over 6 h in a cross-over design. Duodenal biopsies were cultured for 24 h with or without glutamine. Cytokine content of culture media was analysed by ELISA, and the expression of cytokine mRNA in biopsies was assessed by semi-quantitative RT-PCR. **Results:** glutamine given in vivo and in vitro significantly decreased IL-6 [1.4 (0.8-8.5) vs 8.9 (1.0-43.9)] and IL-8 production [5.8 (0-51.4) vs. 53.0 (2.5-114.6), pg/mg wet tissue], median (range), both $< \text{or} = 0.01$, in comparison to no glutamine experiments. Glutamine did not influence IL-4 production. IL-1 β , IL-10 and TNF- α were not detectable in culture media. The expression of any cytokine mRNA was not influenced by glutamine.

CONCLUSIONS: glutamine reduces pro-inflammatory cytokine production by human intestinal mucosa, probably by a post-transcriptional pathway. Glutamine could be useful to modulate inflammatory conditions with imbalanced cytokine production. Copyright 2001 Academic Press.

Increased nitrosothiols in exhaled breath condensate in inflammatory airway diseases.

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Am J Respir Crit Care Med 2001 Mar;163(4):854-858

Nitrosothiols (RS-NOs) are formed by interaction of nitric oxide (NO) with glutathione and may limit the detrimental effect of NO. Because NO generation is increased in airway inflammation, we have measured RS-NOs in exhaled breath condensate in patients with asthma, cystic fibrosis, or chronic obstructive pulmonary disease (COPD). We also measured exhaled NO and nitrite (NO(2-)) in the same subjects. RS-NOs were detectable in exhaled breath condensate of all subjects. RS-NOs were higher in subjects with severe asthma (0.81 0.06 microM) when compared with normal control subjects (0.11 0.02 microM, < 0.01) and with subjects with mild asthma (0.08 0.01 microM, < 0.01). Elevated RS-NOs values were also found in patients with cystic fibrosis (0.35 0.07 microM, < 0.01), in those with COPD (0.24 0.04 microM, $p < 0.01$) and in smokers (0.46 0.09 microM, < 0.01). In current smokers there was a correlation ($r = 0.8$, < 0.05) between RS-NOs values and smoking history (pack/year). We also found elevated concentrations of NO(2-) in patients with severe asthma, cystic fibrosis, or COPD, but not in smokers or patients with mild asthma. This suggests that exhaled NO(2-) is less sensitive than exhaled RS-NOs. This study has shown that RS-NOs are detectable in exhaled breath condensate of healthy subjects and are increased in patients with inflammatory airway diseases. As RS-NOs concentrations in exhaled breath condensate vary in the different airway diseases and increase with the severity of asthma, their measurement may have clinical relevance as a noninvasive biomarker of nitrosative stress.

Can immunoregulatory lactic acid bacteria be used as dietary supplements to limit allergies?

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Studies in gnotobiotic animals have suggested that the intestinal bacterial flora may play an important role in priming the immune system during ontogeny to limit dysfunctional responses, including allergy. Prospective clinical studies have identified a higher incidence of allergy expression in early childhood among children who have low enteric populations of lactic acid bacteria (LAB), such as lactobacilli and bifidobacteria, further supporting a role for gut-colonizing bacteria in regulating immunological atopy. There is some evidence to suggest that supplementing the human diet with probiotic LAB might combat both allergy development and expression of atopy in allergy sufferers; however, definitive information, in the form of controlled intervention trials, remains scant. Recent immunological evidence has indicated that certain strains of LAB can stimulate the production of type I and II interferons and pro-interferon monokines (IL-12 and IL-18), following contact with the immune system; therefore, probiotic forms of immunoregulatory LAB could be used as dietary supplements to modify the gut microflora and provide pro-T helper cell 1 (Th1) STAT-activating signals sufficient to deviate the immune phenotype and correct the Th2-type bias which promotes allergy. This review outlines the clinical and laboratory evidence of a role for LAB in combating allergies, and attempts to explain this phenomenon in terms of our current understanding of immunoregulatory signals produced by gut-colonizing microbes. Copyright 2001 S. Karger AG, Basel

Quercetin inhibits anaphylactic contraction of guinea pig ileum smooth muscle.

Fanning MJ, Macander P, Drzewiecki G, Middleton E Jr.

Int Arch Allergy Appl Immunol 1983;71(4):371-3

Certain flavonoids inhibit antigen-induced release of histamine from mast cells and basophils and also inhibit contraction of guinea pig ileum induced by histamine, acetylcholine, and PGE₂. We examined the effect of one flavonoid, quercetin, on anaphylactic smooth muscle contraction of ileum from guinea pigs sensitized to egg albumin. Quercetin inhibited both the phasic and tonic components of anaphylactic contraction in a concentration-dependent fashion (IC₅₀ approximately 10 microM). Whether this is primarily an effect on mast cell mediator release or inhibition of mediator effects on smooth muscle has not been established.

TPN decreases IL-4 and IL-10 mRNA expression in lipopolysaccharide stimulated intestinal lamina propria cells but glutamine supplementation preserves the expression.

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Shock 2001 Apr;15(4):318-322

Total parenteral nutrition (TPN) decreases intestinal IgA and levels of Th2 cytokines, interleukin (IL)-4, and IL-10 within the supernatants of intestinal homogenates. These cytokines are known to stimulate IgA production in vitro by cells of the gut-associated lymphoid tissue (GALT). Glutamine (GLN) supplementation of TPN normalizes GALT mass and cytokine levels. Because intestinal homogenates contain mucosa which itself is a source of cytokines, it was unclear whether cytokines change within the GALT itself. This study investigates dietary effects on IL-4 and IL-10 cytokine mRNA expression within isolated GALT lamina propria cells after lipopolysaccharide (LPS) stimulation. Prospective randomized experimental trials were used in this study. Fifty-nine mice were randomized to chow, intravenous TPN (IV-TPN), intragastric TPN (IG-TPN), complex enteral diet (CED), or 2% GLN-supplemented TPN (GLN-TPN). In experiment 1, animals were fed chow, IV-TPN, IG-TPN, or CED for 5 days and received intraperitoneal LPS (100 microg/kg BW), and then were sacrificed 1 h later. Intestine was harvested for GALT lamina propria. Total RNA was extracted from lamina propria cells and cytokine mRNA for IL-4, and IL-10 was measured by reverse transcriptase polymerase chain reaction. IgA levels of intestinal washing were also measured with ELISA. In experiment 2, mRNA for IL-4 and IL-10, and intestinal IgA levels were measured in mice fed chow, IV-TPN, or GLN-TPN as in experiment 1. Both IL-4 and IL-10 mRNA expression decreased significantly in IV-TPN mice compared to chow or CED feeding. IG-TPN resulted in IL-10 mRNA expression significantly lower than chow or CED but significantly better than IV-TPN. GLN preserved IL-4 and IL-10 mRNA levels, which correlated with intestinal IgA levels. Route and type of nutrition as well as GLN influence message for the Th2 type IgA-stimulating cytokines, IL-4 and IL-10, within the primary site of GALT IgA production, the lamina propria.

Enrichment of bifidobacteria from human gut contents by oligofructose using continuous culture.

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FEMS Microbiol Lett 1994 May 1;118(1-2):121-127

Chemostat cultures of human faecal bacteria were used to determine the bifidogenic effect of oligofructose, a fermentable carbohydrate found in a number of plants. In single stage continuous culture, oligofructose preferentially enriched for bifidobacteria,

in comparison to sucrose and inulin. This stimulatory effect was enhanced at a high dilution rate, high substrate concentration and low pH. These parameters are likely to approximate to those that occur in the proximal colon. Studies with a three-stage continuous culture model of the large intestine confirmed the bifidogenic effect of oligofructose. These in vitro data indicate that an increase in the concentration of fructose-based oligosaccharides in the diet may alter the balance of the gut microflora towards bifidobacteria, a purported health-promoting genus.

Selective stimulation of bifidobacteria in the human colon by oligofructose and inulin.

Gibson GR, Beatty ER, Wang X, Cummings JH. Medical Research Council, Dunn Clinical Nutrition Centre, Cambridge, England.

Gastroenterology 1995 Apr;108(4):975-982

BACKGROUND/AIMS: Oligofructose and inulin are naturally occurring indigestible carbohydrates. In vitro they selectively stimulate the growth of species of *Bifidobacterium*, a genus of bacteria considered beneficial to health. This study was designed to determine their effects on the large bowel microflora and colonic function in vivo.

METHODS: Eight subjects participated in a 45-day study during which they ate controlled diets. For the middle 15 days, 15 g.day⁻¹ oligofructose was substituted for 15 g.day⁻¹ sucrose. Four of these subjects went on to a further period with 15 g.day⁻¹ inulin. Bowel habit, transit time, stool composition, breath H₂ and CH₄, and the predominant genera of colonic bacteria were measured.

RESULTS: Both oligofructose and inulin significantly increased bifidobacteria from 8.8 to 9.5 log₁₀ g stool⁻¹ and 9.2 to 10.1 log₁₀ g stool⁻¹, respectively, whereas bacteroides, clostridia, and fusobacteria decreased when subjects were fed oligofructose, and gram-positive cocci decreased when subjects were fed inulin. Total bacterial counts were unchanged. Fecal wet and dry matter, nitrogen, and energy excretion increased with both substrates, as did breath H₂. Little change in fecal short-chain fatty acids and breath CH₄ was observed.

CONCLUSIONS: A 15-g.day⁻¹ dietary addition of oligofructose or inulin led to *Bifidobacterium* becoming the numerically predominant genus in feces. Thus, small changes in diet can alter the balance of colonic bacteria towards a potentially healthier microflora.

[Role of polyunsaturated fatty acids in diet therapy of children with allergic diseases]. [Article in Russian]

Gorelova ZI, Ladodo KS, Levachev MM, Lupinovich VL, Mamonova LG, Orlova SV, Balabolkin II, Zadkova GF, Arutiunova MB.

Vopr Pitan 1999;68(1):31-35

135 pediatric patients receiving hypoallergic diet were included into the study group. The control group consisted of 20 children. The impact of PUFA omega-3 biologically active supplements (polyen, prima-Oil) was studied in hypoallergic rations. Biochemical indices were simultaneously investigated. The revealed dynamic changes of fatty acid spectrum in plasma and red cell membranes, cellular and humoral immunity status and eicosanoids synthesis were followed by positive clinical changes. Diets enriched with biologically active supplementation (PUPA omega-3) can be recommended for application in pediatric practice.

Nutritional and pharmacological enhancement of gut-associated lymphoid tissue.

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Can J Gastroenterol 2000 Nov;14:145D-151D

There has been an explosion of research in the field of nutrition over the past quarter century. Clinical studies have demonstrated the effectiveness of providing nutrition by the enteral route in reducing septic morbidity in critically ill patients. These improved outcomes have been substantiated by animal models that show that enteral nutrition decreases gut permeability while maintaining the gut-associated lymphoid tissue (GALT) in mucosal immunity. Evidence points to the important immunological role of the gut in the maintenance of mucosal immunity at both intestinal and extraintestinal sites. The preservation of this mucosal immunity by enteral nutrition is consistent with the lower morbidity seen in severely injured patients who receive nutrition via the gastrointestinal tract. For patients who are unable to be fed by the enteral route and who require parenteral nutrition, several supplements show promise in enhancing the mucosal immune system defenses. The nutritional and pharmacological tactics that may enhance the GALT and thereby maintain mucosal immunity are examined.

Diet and childhood asthma in a society in transition: a study in urban and rural Saudi Arabia.

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Thorax 2000 Sep;55(9):775-779

BACKGROUND: The causes of the worldwide increases in asthma and allergic diseases in childhood, which seem to relate to increasing prosperity, are unknown. We have previously hypothesised that a reduction in the antioxidant component of the diet is an important factor. An investigation was undertaken of dietary and other risk factors for asthma in Saudi Arabia where major lifestyle differences and prevalences of allergic disease are found in different communities.

METHODS: From a cross sectional study of 1444 children with a mean age of 12 (SD 1) years in Jeddah and a group of rural Saudi villages, we selected 114 cases with a history of asthma and wheeze in the last 12 months and 202 controls who had never complained of wheeze or asthma, as recorded on the ISAAC questionnaire. Risk factors for asthma and allergies (family history, social class, infections, immunisations, family size, and diet) were ascertained by questionnaire. Atopy was assessed by skin prick testing.

RESULTS: In univariate analyses, family history, atopy, and eating at fast food outlets were significant risk factors for wheezy illness, as were the lowest intakes of milk and vegetables and of fibre, vitamin E, calcium, magnesium, sodium, and potassium. These differences were present also in the urban children considered separately. Sex, family size, social class, infections, and parental smoking showed no relationship to risk. In multiple logistic regression analysis, urban residence, positive skin tests, family history of allergic disease, and the lowest intakes of vitamin E, magnesium and sodium related significantly and independently to risk. The lowest tertile of intake of vitamin E was associated with a threefold (95% CI 1.38 to 6.50) increase in risk when adjusted for the other factors. Intake of milk and vegetables both showed inverse linear relationships to being a case.

CONCLUSIONS: This study suggests that dietary factors during childhood are an important influence in determining the expression of wheezy illness, after allowing for urban/rural residence, sex, family history, and atopy. The findings are consistent with previous studies in adults and with the hypothesis that change in diet has been a determinant of the worldwide increases in asthma and allergies.

Probiotics in primary prevention of atopic disease: a randomized placebo-controlled trial.

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Lancet 2001 Apr 7;357(9262):1076-1079

BACKGROUND: Reversal of the progressive increase in frequency of atopic disease would be an important breakthrough for health care and wellbeing in western societies. In the hygiene hypothesis this increase is attributed to reduced microbial exposure in early life. Probiotics are cultures of potentially beneficial bacteria of the healthy gut microflora. We assessed the effect on atopic disease of *Lactobacillus GG* (which is safe at an early age and effective in treatment of allergic inflammation and food allergy).

METHODS: In a double-blind, randomised placebo-controlled trial we gave *Lactobacillus GG* prenatally to mothers who had at least one first-degree relative (or partner) with atopic eczema, allergic rhinitis, or asthma, and postnatally for 6 months to their infants. Chronic recurring atopic eczema, which is the main sign of atopic disease in the first years of life, was the primary endpoint.

FINDINGS: Atopic eczema was diagnosed in 46 of 132 (35%) children aged 2 years. Asthma was diagnosed in six of these children and allergic rhinitis in one. The frequency of atopic eczema in the probiotic group was half that of the placebo group (15/64 [23%] vs 31/68 [46%]; relative risk 0.51 [95% CI 0.32-0.84]). The number needed to treat was 4.5 (95% CI 2.6-15.6).

INTERPRETATIONS: *Lactobacillus GG* was effective in prevention of early atopic disease in children at high risk. Thus, gut microflora might be a hitherto unexplored source of natural immunomodulators and probiotics, for prevention of atopic disease.

Dietary fatty acids and allergy.

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Ann Med 1999 Aug;31(4):282-287

The increase in the prevalence of atopic diseases has recently been linked to altered consumption of polyunsaturated fatty acids (PUFAs). As typical Western diets contain almost 10 times more linoleic acid (18:2 omega-6) than alpha-linolenic acid (18:3 omega-3), it is the metabolism of the former that predominates. Subsequently produced arachidonic acid-derived eicosanoids alter

the balance of T-helper cells type 1 and type 2 thus favouring the production of immunoglobulin (Ig)E. In atopic subjects, the impact of this excessive eicosanoid production may be further strengthened as a result of changes in cyclic nucleotide metabolism exacerbated by substrate availability. Dietary omega-3 fatty acids can have marked influence on both specific and nonspecific immune responses in modifying eicosanoid production and replacing omega-6 fatty acids in cell membranes. Therefore, it is concluded that careful manipulation of dietary PUFAs may play a key role in the successful management of inflammation associated with atopic diseases.

Polyunsaturated fatty acids in maternal diet, breast milk, and serum lipid fatty acids of infants in relation to atopy.

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Allergy 2001 Jul;56(7):633-638

BACKGROUND: The increased consumption of n-6 polyunsaturated fatty acids (PUFA) has been shown to coincide with the increased prevalence of atopic diseases. We aimed to investigate whether maternal diet and atopic status influence the PUFA composition of breast milk and the serum lipid fatty acids of infants.

METHODS: Maternal diet was assessed by a food questionnaire. The PUFA composition of breast milk obtained at 3 months from 20 allergic and 20 healthy mothers and of their infants' (10 atopic and 10 nonatopic/group of mothers) serum lipids was analyzed.

RESULTS: Although no differences in maternal PUFA intake were observed, the breast milk of allergic mothers contained less gamma-linolenic acid (18:3 n-6) than that of healthy mothers. Similarly, atopic infants had less gamma-linolenic acid in phospholipids than healthy infants, although n-6 PUFA were elevated in other serum lipid fractions in atopic infants. The serum lipid fatty acids in atopic infants did not correlate with those in maternal breast milk.

CONCLUSION: Our results suggest that dietary n-6 PUFA are not as readily transferred into breast milk or incorporated into serum phospholipids, but may be utilized for other purposes, such as eicosanoid precursors, in allergic/atopic individuals. Subsequently, high dietary proportions of n-6 PUFA, or reduced proportions of regulatory PUFA, such as gamma-linolenic acid and n-3 PUFA, may be a risk factor for the development of atopic disease.

Aloe vera.

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J Am Acad Dermatol 1988 Apr;18(4 Pt 1):714-720

We review the scientific literature regarding the aloe vera plant and its products. Aloe vera is known to contain several pharmacologically active ingredients, including a carboxypeptidase that inactivates bradykinin in vitro, salicylates, and a substance (s) that inhibits thromboxane formation in vivo. Scientific studies exist that support an antibacterial and antifungal effect for substance(s) in aloe vera. Studies and case reports provide support for the use of aloe vera in the treatment of radiation ulcers and stasis ulcers in man and burn and frostbite injuries in animals. The evidence for a potential beneficial effect associated with the use of aloe vera is sufficient to warrant the design and implementation of well-controlled clinical trials.

Glutamine-enriched total parenteral nutrition maintains intestinal interleukin-4 and mucosal immunoglobulin A levels.

Kudsk KA, Wu Y, Fukatsu K, Zarzaur BL, Johnson CD, Wang R, Hanna MK. University of Tennessee, Memphis, USA.

JPEN J Parenter Enteral Nutr 2000 Sep;24(5):270-274

BACKGROUND: Total parenteral nutrition (TPN) prevents progressive malnutrition but fails to maintain intestinal gut-associated lymphoid tissue (GALT) or established respiratory antiviral or antibacterial mucosal immunity. Our previous work demonstrated that decreases in intestinal immunoglobulin A (IgA) were associated with decreases in Th2-type IgA-stimulating cytokines, interleukin (IL)-4 and IL-10. Because glutamine supplementation of TPN partially preserves respiratory defenses and normalizes GALT, we investigated the ability of parenteral glutamine to normalize respiratory and intestinal IgA levels and measured Th2 cytokines in intestinal homogenates.

METHODS: Animals were cannulated and randomly assigned to receive chow (n = 17), TPN (n = 18), or an isonitrogenous, isocaloric TPN solution formulated by removing the appropriate amount of amino acids and replacing them with 2% glutamine (n = 18) for 5 days. Respiratory tract and intestinal washings were obtained for IgA and the intestine homogenized and analyzed for IL-4 and IL-10.

RESULTS: TPN decreased intestinal and respiratory IgA in association with decreases in intestinal IL-4 and IL-10 compared with chow-fed animals. Glutamine significantly improved respiratory and intestinal IgA levels, significantly improved IL-4 compared with TPN animals, and maintained IL-10 levels midway between chow-fed and TPN animals.

CONCLUSIONS: Glutamine-enriched TPN preserved both extraintestinal and intestinal IgA levels and had a normalizing effect on Th2-type IgA-stimulating cytokines.

Oligosaccharides in human milk: structural, functional, and metabolic aspects.

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Annu Rev Nutr 2000;20:699-722

Research on human milk oligosaccharides (HMOs) has received much attention in recent years. However, it started about a century ago with the observation that oligosaccharides might be growth factors for a so-called bifidus flora in breast-fed infants and extends to the recent finding of cell adhesion molecules in human milk. The latter are involved in inflammatory events recognizing carbohydrate sequences that also can be found in human milk. The similarities between epithelial cell surface carbohydrates and oligosaccharides in human milk strengthen the idea that specific interactions of those oligosaccharides with pathogenic microorganisms do occur preventing the attachment of microbes to epithelial cells. HMOs may act as soluble receptors for different pathogens, thus increasing the resistance of breast-fed infants. However, we need to know more about the metabolism of oligosaccharides in the gastrointestinal tract. How far are oligosaccharides degraded by intestinal enzymes and does oligosaccharide processing (e.g. degradation, synthesis, and elongation of core structures) occur in intestinal epithelial cells? Further research on HMOs is certainly needed to increase our knowledge of infant nutrition as it is affected by complex oligosaccharides.

[Effects of ginkgo leave concentrated oral liquor in treating asthma]. [Article in Chinese]

Li MH, Zhang HL, Yang BY. Qingdao Hospital of Integrated Traditional and Western Medicine, Shandong.

Zhongguo Zhong Xi Yi Jie He Za Zhi 1997 Apr;17(4):216-218

OBJECTIVE: To determine the effects of Ginkgo leave concentrated oral liquor (GLC) on airway inflammation.

METHODS: Airway hyperreactivity and clinical symptoms and pulmonary functions of asthma patients were determined.

RESULTS: In contrast to placebo group, GLC significantly reduced airway hyperreactivity (< 0.05) and improved clinical symptoms (< 0.05), pulmonary functions (< 0.05) of the asthmatic patients.

CONCLUSION: GLC is an effective drug of anti airway inflammation.

In vitro effects of Ginkgolide B on lymphocyte activation in atopic asthma: comparison with cyclosporin A.

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Jpn J Pharmacol 2000 Jul;83(3):241-245

The effects of Ginkgolide B (BN52021) on in vitro activation responses of human peripheral blood mononuclear cells (PBMC) from asthmatic patients was measured using 2-channel flow cytometric analysis of activation-associated cell surface antigens or ELISA assays for cytokines known to be expressed by PBMC during T1 or T2 immunological activation. BN52021 is an anti-inflammatory extract of Ginkgo biloba and has been used therapeutically. It is a known inhibitor of platelet activating factor (PAF), which is important in the pathogenesis of asthma, and may synergise with cyclosporin A (CyA) to inhibit pathogenic immune activation in asthmatics. We compared the inhibitory effects of BN52021 and CyA (1 microM each) on activation of PBMC of asthmatic patients stimulated by phorbol myristate acetate and calcium ionophore. Inhibition of production of the cytokines IL-4 and IL-5 by BN52021 was insignificant compared to CyA. However, BN52021 significantly reversed the increase in activation-associated CD45RA expression, with a trend towards decreased expression of HLA-DR. Lymphocyte activation markers were not significantly altered by CyA. Since they appear to have differing effects on activated cells, the anti-inflammatory effects of CyA and BN52021 in atopic asthma is potentially additive. The present approach may be useful for preliminary evaluation of novel therapeutic modalities for asthma treatment.

Study of the effect of *Lactobacillus paracasei* and fructooligosaccharides on the faecal microflora in weanling piglets.

Nemcova R, Bomba A, Gancarcikova S, Herich R, Guba P Research Institute of Veterinary Medicine, Kosice, Slovak Republic.

Berl Munch Tierarztl Wochenschr 1999 Jun-Jul;112(6-7):225-8

The influence of administration of *Lactobacillus paracasei* alone and mixture of *Lactobacillus paracasei* and fructooligosaccharide on faecal bacteria counts in the weanling pigs was investigated. The administration of *Lactobacillus paracasei* alone significantly decreased *Clostridium* (< 0.05) and *Enterobacteriaceae* (< 0.05) counts as compared to the control. *Lactobacillus paracasei* administered in combination with fructooligosaccharide significantly increased *Lactobacillus* (< 0.01-< 0.05), *Bifidobacterium* (< 0.05), total anaerobes (< 0.05), and total aerobes (< 0.05) counts compared to control group as well as *Lactobacillus paracasei* group and significantly decreased *Clostridium* (< 0.05) and *Enterobacteriaceae* (< 0.01) counts compared to control group. The results obtained point out to a synergic effect of the combination of *Lactobacillus paracasei* and fructooligosaccharide on numbers of bacterial populations observed in the faeces of the weanling pigs.

Brainrecovery.Com: Powerful Therapy for Challenging Brain Disorders

Perlmutter, D.

2000 May 1. Naples, FL: Publisher David Perlmutter (ISBN 0963587412).

Clinical applications of probiotic agents.

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Am J Clin Nutr 2001 Jun;73(6):1147S-1151S

In the past century the beneficial roles of nonpathogenic bacteria in the intestinal lumen were described. In the past decade there has been a dramatic increase in scientific work supporting the concept that there are clinical benefits to ingesting specific nonpathogenic organisms (probiotics). The potential benefits of modifying the intestinal flora composition of certain high-risk groups, eg, premature infants, travelers, and children receiving antibiotics, are emerging in the literature. Studies documenting prophylactic and therapeutic benefits in acute viral gastroenteritis and in atopic disease point not only to the potential applications, but also to the fact that the mechanisms of action of these agents may be due to their interaction with the gut as an immunologic organ. The benefits documented thus far are of varying degree and are most likely dependent on the number of agents, the dose, the dosing patterns, and the characteristics of the host and its underlying luminal microbial environment. Consequently, the safety and specification of a particular probiotic agent and methods of delivery to a particular population for a particular purpose should be carefully documented before making broad recommendations. The cost-benefit assessment of adding probiotics to our diet for prophylactic or therapeutic purposes, as well as better regulation of these agents as commercial products, is also needed.

Consequences of magnesium deficiency on the enhancement of stress reactions; Preventive and therapeutic implications (A review)

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J. Am. Coll. Nutr. (USA), 1994, 13/5 (429-446)

Stress intensifies release of catecholamines and corticosteroids that increase survival of normal animals when their lives are threatened. When magnesium (Mg) deficiency exists, stress paradoxically increases risk of cardiovascular damage including hypertension, cerebrovascular and coronary constriction and occlusion, arrhythmias and sudden cardiac death (SCD). In affluent societies, severe dietary Mg deficiency is uncommon, but dietary imbalances such as high intakes of fat and/or calcium (Ca) can intensify Mg inadequacy, especially under conditions of stress. Adrenergic stimulation of lipolysis can intensify its deficiency by complexing Mg with liberated fatty acids (FA). A low Mg/Ca ratio increases release of catecholamines, which lowers tissue (i.e. myocardial) Mg levels. It also favors excess release or formation of factors (derived both from FA metabolism and the endothelium), that are vasoconstrictive and platelet aggregating; a high Ca/Mg ratio also directly favors blood coagulation, which is also favored by excess fat and its mobilization during adrenergic lipolysis. Auto-oxidation of catecholamines yields free radicals, which explains the enhancement of the protective effect of Mg by anti-oxidant nutrients against cardiac damage caused by beta-catecholamines. Thus, stress, whether physical (i.e. exertion, heat, cold, trauma-accidental or surgical, burns), or emotional (i.e. pain, anxiety, excitement or depression) and dyspnea as in asthma increases need for Mg. Genetic differences in Mg utilization may account for differences in vulnerability to Mg deficiency and differences in body responses to stress.

Continuous culture selection of bifidobacteria and lactobacilli from human faecal samples using fructooligosaccharide as selective substrate.

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J Appl Microbiol 1998 Oct;85(4):769-77

The human large intestine contains a large and diverse population of bacteria. Certain genera, namely *Bifidobacterium* and *Lactobacillus*, are thought to exert health-promoting effects. Prebiotics such as fructooligosaccharides (FOS) have been shown to stimulate the growth of endogenous bifidobacteria. In this study, changes of lactic acid producing bacteria in continuous culture fermentors (semi-defined, anaerobic medium containing 5 g l⁻¹ FOS, dilution rate of 0.1 h⁻¹, pH 5.5) were followed over a 21 d period after inoculation with blended human faeces from four healthy adults. Samples were also taken every 3 d for influent/effluent FOS, short chain fatty acid (SCFA), lactate and microbiological analyses. Results showed that SCFA concentrations decreased abruptly 1 d after inoculation while lactate concentrations increased. Classical methods of enumeration using selective media showed that the proportion of total culturable count represented by bifidobacteria and lactobacilli increased from 11.9% on day 1 to 98.1% on day 21. However, molecular methods using genus-specific 16S rRNA oligonucleotide probes indicated that the bifidobacterial population maintained a level between 10 and 20% of total 16S rRNA during the first 6 d and disappeared rapidly when the maximum concentration of lactate was reached. Lactobacilli, which were initially present in low numbers, increased until day 9 and remained at high levels (20-42% of total 16S rRNA) to day 21, with the exception of day 18. Although FOS has usually been regarded as a selective substrate for bifidobacteria, these observations suggest that: (1) lactobacilli are also able to use FOS, (2) lactobacilli can out-compete bifidobacteria in continuous culture at pH 5.2-5.4 when FOS is the primary carbon and energy source, and (3) bifidobacteria can grow faster on FOS than lactobacilli under controlled conditions.

Protective effect of bifidus milk on the experimental infection with *Salmonella enteritidis* subsp. *typhimurium* in conventional and gnotobiotic mice.

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J Appl Microbiol 1999 Feb;86(2):331-336

The ability of *Bifidobacterium bifidum* from a commercial bifidus milk to antagonize *Salmonella enteritidis* subsp. *typhimurium* in vivo, and to reduce the pathological consequences for the host, was determined using conventional and gnotobiotic mice. Conventional animals received daily, by gavage, 0.1 ml bifidus milk containing about 10(9) cfu *B. bifidum* and germ-free animals received a single 0.1 ml dose. The conventional and gnotobiotic groups were challenged orally with 10(2) cfu of the pathogenic bacteria 5 and/or 10 d after the beginning of treatment. Control groups were treated with milk. Bifidus milk protected both animal models against the challenge with the pathogenic bacteria, as demonstrated by survival and histopathological data. However, to obtain the protective effect in gnotobiotic animals, the treatment had to be initiated 10 d before the challenge. In experimental and control gnotobiotic mice, *Salm. enteritidis* subsp. *typhimurium* became similarly established at levels ranging from 10(8) to 10(9) viable cells g⁻¹ of faeces and remained at these high levels until the animals died or were sacrificed. It was concluded that the protection against *Salm. enteritidis* subsp. *typhimurium* observed in conventional and gnotobiotic mice treated with bifidus milk was not due to the reduction of the intestinal populations of the pathogenic bacteria.

[Effects of oral administration of bifidobacteria on intestinal microflora in premature and newborn infants]. [Article in German]

Uhlemann M, Heine W, Mohr C, Plath C, Pap S. Kinder- und Jugendklinik der Universitat Rostock.

Z Geburtshilfe Neonatol 1999 Sep;203(5):213-217

In a prospective, randomised study the effects of orally administered bifidobacteria on the intestinal microflora were investigated in 100 preterm and term neonates under intensive care conditions during the first 21 days of life. The 50 infants (group with bifidobacteria) received lyophilized bifidobacteria (Topfer Bifidus) via nasogastral tube with an initial dosage of 3 times daily 1.25 x 10⁸ bifidobacteria on day 2 of life and a daily dosage of 6 times 1.25 x 10⁸ bifidobacteria on day 3 until day 21 of life. The other 50 infants (control group) did not receive bifidobacteria. The preterm and term neonates were fed either with pasteurized mother's milk or milk from healthy female donors (n = 79) or with an infant formula (Alfare, n = 13) or initially with Alfare and thereafter with mother's milk (n = 8). The intestinal microflora of preterm and term neonates under intensive care conditions could be influenced by the oral administration of bifidobacteria. The administration of bifidobacteria resulted in the group of inoculated infants in a significantly earlier colonization of bifidobacteria (8.1 ± 3.9 days of life) than in the control group (11.3 ± 4.7 days of life). On day 7 a bifidobacterial dominance (< 90% of the intestinal microflora) could be found in 26% of infants with inoculation of bifidobacteria and only in 2% of the control group (< 0.001). These significant differences could be shown until day 21 of life. A difference in septicemia

frequency between the two groups could not be demonstrated. At the beginning of the infection a bifidobacterial dominance was found in only one of 23 cases of septicemia.

The effect of a newly developed ointment containing eicosapentaenoic acid and docosahexaenoic acid in the treatment of atopic dermatitis.

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J Med Invest 1999 Aug;46(3-4):173-177

While various therapeutic modalities have been tried for atopic dermatitis (AD), numerous obstinate cases exist in which sufficient effects cannot be obtained. Therefore, we developed and prepared an ointment containing docosahexaenoic acid and eicosapentaenoic acid as a topical therapeutics for AD. We applied this ointment to 64 patients with AD (aged between 2 months and 29 years) who showed poor responses to conventional therapies and obtained satisfactory results. This ointment is considered a new topical preparation for AD.

Immune senescence and adrenal steroids: Immune dysregulation and the action of dehydroepiandrosterone (DHEA) in old animals

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Eur J Clin Pharmacol 1993;45 Suppl 1:S21-3; discussion S43-4

Immune senescence is characterized by dysregulation of the immune system. The disorder occurs during old age and is manifested by an increased production of autoantibodies and a decreased production of antibodies to most foreign antigens. These events seem to reflect an altered ratio of activity between the CD5+ and CD5- B cell subsets. Likewise, there is dysregulation of cytokine production with an increased production of IL-4, IL-5 and IL-6 associated with a decreased production of IL-2. This appears to reflect an altered ratio of activity between the Th1 and Th2 cell subsets. Dehydroepiandrosterone (DHEA) is one of the three principal adrenal steroids; its serum concentration declines with age. Recent results suggest that in vitro culture of lymphocytes, from aged donors, with DHEA or in vivo treatment of old mice with DHEA sulphate results in the augmentation of the antibody response to foreign antigens and a reversal in the dysregulated cytokine production by T cells. Thus, a decline in one of the three principal adrenal steroids is associated with age-associated changes in the immune system. Some of these changes can be reversed by exposure to DHEA.

Reduced levels of glutathione S-transferases in patch test reactions to dithranol and sodium lauryl sulphate as demonstrated by quantitative immunocytochemistry: evidence for oxidative stress in acute irritant contact dermatitis.

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Eur J Dermatol 2001 Mar;11(2):99-104

There is increasing evidence that oxidative stress plays a role in the pathogenesis of acute irritant contact dermatitis. As part of on-going studies into the effect of irritant chemicals on the anti-oxidant enzyme systems in the skin, we have examined the changing levels of two classes of glutathione S-transferase in patch test reactions to dithranol and sodium lauryl sulphate, using quantitative immunocytochemistry. Although no changes were evident after 6 hrs, significant reductions in the density of staining for glutathione S-transferase alpha were seen with both irritants after 48 hrs and 96 hrs. Glutathione S-transferase pi levels were reduced to a lesser degree, reaching significance for dithranol at the 96 hrs time point only, and for sodium lauryl sulphate at 48 hrs only. The results support the hypothesis that oxidative stress plays a role in chemically-induced inflammation, not only in the case of irritants such as dithranol which are known to directly generate reactive oxygen species, but also with chemicals not generally associated with free radical generation.

Metabolic support of the gastrointestinal tract: potential gut protection during intensive cytotoxic therapy.

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Cancer 1997 May 1;79(9):1794-1803

BACKGROUND: Potentially curative options involving cytoablative therapies are now available for the treatment of almost all human tumors, but major toxicities represent the rate-limiting step in achieving a cure with these therapies. With successful

hematoprotective strategies now in use, it is apparent that the gastrointestinal tract will be the rate-limiting organ system that prevents further dose escalation in many cancer patients.

METHODS: A review of the English language literature was conducted. Paperchase, a computer-based application that reviews the data bases of the National Library of Medicine and the National Cancer Institute, was used to obtain pertinent literature.

RESULTS: A variety of gut-protective nutrients and growth factors were identified. These substances may be useful in preventing dose-limiting gastrointestinal symptoms. Animal studies and some patient data suggest that the amino acid glutamine stimulates mucosal growth and promotes gut health. When nutrient administration is coupled with growth factors, such as growth hormone, insulin-like growth factor-1, glucagon-like peptide-2, and interleukin-11, a high level of bowel protection should be attained.

CONCLUSIONS: Therapy is evolving that may be useful in protecting the intestinal mucosa and preventing dose-limiting gastrointestinal symptoms.

A modified determination of coenzyme Q10 in human blood and CoQ10 blood levels in diverse patients with allergies.

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Biofactors 1988 Dec;1(4):303-6

Two situations required a modified determination of coenzyme Q10 (CoQ10) in human blood and organ tissue. Blood from patients with AIDS and cancer raised apprehensions about safety to an analyst, and the number of specimens for analysis is increasing enormously. A modified determination replaces silica gel-TLC with disposable Florisil columns, and steps were simplified to allow more analyses per unit time. Data from the modified determination are quantitatively compatible with data from older and tedious procedures. This determination was used for blood from 36 diverse patients with allergies. The mean CoQ10 blood level of these patients is not different from the mean level of so-called normal individuals, but approximately 40% (14/36) of these allergic patients had levels up to 0.65 micrograms/ml, which is the level of dying class IV cardiac patients. The biosynthesis of CoQ10 in human tissues is a complex process that requires several vitamins and micronutrients, so that countless vitamin-unsupplemented Americans may be deficient in CoQ10. The relationship of allergies to autoimmune mechanisms and immunity, and the established relationship of CoQ10 to immune states, may be a rationale for therapeutic trials of administering CoQ10 to patients with allergies who have low CoQ10 blood levels and are very likely deficient.

The scientific rediscovery of an ancient Chinese herbal medicine: Cordyceps sinensis: part I.

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J Altern Complement Med 1998 Fall;4(3):289-303

This review presents *Cordyceps sinensis* (Berk.) Sacc., a fungus highly valued in China as a tonic food and herbal medicine. The extant records show the continued use of *C. sinensis* is now centuries old. The major chemical, pharmacological, and toxicological studies on *C. sinensis* and the various derived, cultured, fermented mycelial products currently in use are reviewed from the English and Chinese literature. Preclinical in vitro and in vivo studies and clinical blinded or open-label trials in to date over 2000 patients are reviewed. These studies show the main activities of the fungus in oxygen-free radical scavenging, antisenescence, endocrine, hypolipidemic, antiatherosclerotic, and sexual function-restorative activities. The safety of the fungus, its effects on the nervous system, glucose metabolism, the respiratory, hepatic, cardiovascular, and immune systems, immunologic disease, inflammatory conditions, cancer, and diseases of the kidney will be reviewed in the second part of this article to be published in the winter issue of this journal.

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